

# DICTIONARY OF BIO-CHEMISTRY AND RELATED SUBJECTS

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## ... Preface ...

The Dictionary of Biochemistry is a pioneering effort in an entirely new field. There have been no previous dictionaries of this kind. Furthermore, the concept of a "dictionary" has been changing from that of a mere alphabetical glossary to something resembling an encyclopedia. At least a dozen of conflicting possibilities offered themselves at the planning of this volume, each of which was both enthusiastically supported and violently attacked by people with strong preferences and aversions. There was only one thing left to do and that was to try to reconcile seeming contradictions and to combine as many features as possible. All of this had to be done within serious limitations of space and serious limitations of cooperation due to the outbreak of the war. Consequently, this effort breaks ground in many directions. The dictionary contains a great deal of glossary material and also a great deal of fairly lengthy authoritative discussion. It tries to maintain a balance between obsolescent, established and newly explored material. It is designed for readers of biochemical literature who might want the definitions of terms used more than a decade ago as well as of terms just coined. There was no intention of replacing text-books or abstract or review journals, except insofar as certain items are greatly neglected or are not easily available. This will account for what might appear as too liberal an allowance for articles on teeth, hair, biochemistry of psychiatry, phosphate bond energy, bacteriophage, etc., and a corresponding brevity on topics found in every text. Articles, like Prof. Witzemann's unified discussion of carbohydrate and fat metabolism, also represent an effort at something different, highly synthetic in the midst of the atomism of a dictionary.

It is highly fitting that a scientific dictionary should itself be experimental. In view of this we earnestly request suggestions from workers in the field, be they experts or students, and from workers from neighboring fields who might want to receive or give information from their point of view. Our criteria must change with growing experience in the actual practical use of the dictionary.

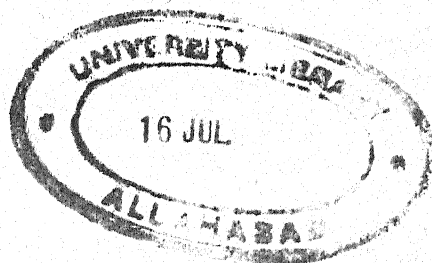
We take this occasion to thank the collaborators, whose names are listed separately; to acknowledge the fine courtesy of Dr. R. E. Gruber, Vice-Pres. of Merck & Co., who granted permission to select data from *The Merck Index* (Fifth Ed.) and *The Merck Manual* (Seventh Ed.), and of the Science Press and Chas. C. Thomas, Publisher, who allowed the reprinting of article and text material; and to express appreciation of the technical advice of Dr. Dagobert D. Runes.

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## A

### A

See Angstrom Unit.

### ABDERHALDEN'S ANHYDRIDE THEORY

In the 1920's, Abderhalden pointed out that much of the behavior of proteins is better explained on the basis of a structure of diketopiperazine rings held together by latent valences, than on straight chain polypeptides. He was able to obtain a number of these cyclic anhydrides of amino acids from protein hydrolysis products.

### ABDERHALDEN-SCHMIDT TEST FOR PROTEINS AND THEIR DECOMPOSITION PRODUCTS

One to two drops of reagent, made by dissolving 0.1 gm. of ninhydrin in 300 cc of water, is added to the test solution and heated. The presence of a protein, polypeptide, amino acid or peptone is indicated by a blue color. Reagent may also be used in pregnancy diagnosis.

Reference: Zeit. physiol. Chem. 72, 37; 85, 143. Münch. med. Wochschr. 1912. 1305, 1940; 1913, 1402. Weiss. ibid. 1925, 2238.

### ABDERHALDEN TEST FOR CYSTINE

A reaction depending on the formation of naphthalenesulfocystine by treating cystine with beta-

naphthalenesulfochloride in NaOH.

### ABDOMEN

Section of trunk behind thorax which contains the viscera; belly; pygidium.

### ABDOMINAL REGIONS

The nine areas of the abdomen formed by intersection of two pairs of horizontal and vertical lines, namely hypochondriac, lumbar, inguinal, epigastric, hypogastric and umbilical.

### ABDUCENS

Sixth cranial nerve supplying lateral rectus muscle of eyeball.

### ABDUCTOR MUSCLE

Muscle causing movement away from main axis.

### ABEL-DRECHSEL TEST FOR CARBAMIC ACID

The acid, in urine, is converted to the calcium salt, from which calcium carbonate precipitates on standing and which evolves ammonia upon boiling.

Reference: Skand. Arch. Physiol. 1891, 236. Zeit. anal. Chem. 32, 513 (1893).

### ABELIN REACTION FOR ARSPHENAMINE

Arsphenamine is dissolved in 100 cc of water and 4 drops of dilute hydrochloric acid; solution cooled and treated with 0.5% aqueous solution of sodium nitrate yield

ing an intensely greenish yellow fluorescence. When poured into 10% alkaline resorcinol solution, a red color is obtained.

Reference: Münch. Med. Wochschr. 1910, 1002. Pellerin, Bull. sci. pharmacol. 33, 205 (1926).

#### ABELIN TEST FOR NEOARSPHENAMINE

Neoarsphenamine in urine is detected by splitting off formaldehyde.

Urine, not older than 3-4 hours and preferably collected within ½-1 hour after injection is used. 10-15 cc. are treated with a freshly prepared and filtered 1% solution of phenylhydrazine hydrochloride. After cooling 1 cc. of freshly prepared 5% potassium ferrocyanide solution is added. If formaldehyde is present, a fuchsin-red color is developed upon the addition of 5 cc. of concentrated hydrochloric acid. Dilution with an equal volume of water and extraction with ether renders the test more sensitive, a yellow color being obtained in the extract which turns red when hydrochloric acid is added.

Reference: Arch. exptl. Path. Pharmacol. 75, 320 (1914).

#### ABIETIC ACID

Sylvic acid; a diterpene acid,  $C_{20}H_{30}O_2$ , the chief constituent of rosin; assists in the growth of lactic and butyric acid ferments.

#### ABIOGENESIS

The origin of living matter from organic colloid matter in conjunction with inorganic components under suitable conditions in the evolution of the earth.

#### ABOMASIUM

Final or true ruminant stomach.

#### ABORT

(1) to give birth to a dead foetus;

(2) to arrest development.

#### ABRIN

Toxalbumin; agglutinin; probably a mixture of two toxic proteins found in *Abrus precatorius*, an Indian shrub; used in extremely dilute solution in trachoma.

#### ABSORPTION

The penetration of a liquid or solid into or through another liquid or solid, the particles that are absorbed being molecular or micellar in size.

#### ABSORPTION, INTESTINAL

e.g. of carbohydrates, it is a function of the species, selectivity of mucosa, presence of other substances, enzyme activity involving phosphorylation, circulation of the blood supply as well as the nature of the substance absorbed.

#### ACAIIN

See Flavone Glycosides.

#### ACALCEROSIS

Calcium deficiency.

#### ACANTHIN

Substance forming skeleton of radiolarians.

#### ACAPNIA

Carbon dioxide deficiency.

#### ACCEPTOR

A substance which can be oxidized by oxygen or reduced by hydrogen only in the presence of another substance undergoing a similar reaction.

#### ACCESSORY CHROMOSOMES

See Chromosomes.

#### ACCRETION

Growth by outer addition.

#### ACENAPHTHENE

DERIVATIVES, ESTROGENIC ACTIVITIES OF

See Estrogens, Synthetic.

**ACERATE**

Sharp.

**ACEROULUS**

Sandy material in brain, essentially magnesium ammonium phosphate; corpora amylacea.

**ACETABULUM**

Socket for head of a leg or a bone.

**ACETALDEHYDE**

**REDUCTASE**

An enzyme which catalyzes the reduction of acetaldehyde to alcohol, similar in structure to the yellow respiratory enzyme.

**ACETANNIN**

Diacetyl tannic acid; used as intestinal astringent.

**ACETIC ACID**

See Detoxication.

**ACETOACETIC ACID**

$\text{CH}_3\text{COCH}_2\text{COOH}$ ; diacetic acid; a keto-fatty acid found in fermentation and as an intermediate of metabolism; b.p.  $180^\circ$ .

**ACETOACETIC ACID TESTS, IN URINE**

See Arnold, Bondi-Schwarz, Morner.

**ACETOIN**

Acetyl methyl carbinol; produced by acetic acid bacteria from glycols.

**ACETOL**

Hydroxyacetone; b.p.  $145-6^\circ$ ; produced by *B. xylinum* from propylene glycol.

**ACETONE BODIES**

Ketonic bodies formed in urine and blood in absence of carbohydrate oxidation, such as in diabetes mellitus or fasting; acetone, acetoacetic acid and beta-hydroxybutyric acid.

**ACETONE TESTS, IN URINE**

See Barrett, Baeyer-Drewsen,

Bülow, Deniges, Faught, Fabinyi, Legal, Wagenaar.

**ACETOPHENETIDINE**

See Phenacetin.

**ACETYLBENZOYLACONINE**

See Aconitine.

**ACETYLCHOLINE**

Acetyl-trimethyl- $\beta$ -hydroxyethyl-ammonium hydroxide, a compound which along with sympathin (q.v.) is involved in the transmission of nerve impulses across certain junctional regions, as from parasympathetic nerve to heart.

See Bioelectric Potentials.

**ACETYL NUMBER (acetyl value)**

The number of milligrams of potassium hydroxide needed to neutralize the acetic acid liberated by the hydrolysis of 1 gm. of acetylated fat or oil; used as an indication of the number of hydroxyl groups present.

**ACETYL VALUE**

See Acetyl Number.

**ACHILLIS TENDO**

The hamstring.

**ACHLORHYDRIA**

An acidity; a failure to secrete free HCl which in some cases is counteracted by histamine injection; incidence increases with advancing age and involves anemia and possibly arthritis.

**ACHONDROPLASIA**

A condition of dwarfism due to cartilage deficiency with stunted limbs but normal trunk.

**ACHROGLOBIN**

Colorless respiratory pigment of some molluscs and tunicates; chemical nature and even reality of existence are doubtful.



**ACHROMATIN**

The non-staining substance of the nucleus.

**ACHROÖDEXTRIN**

A polysaccharide formed on partial hydrolysis of starch with amylase; gives no color with iodine.

**ACHYLIA**

See Gastro-Enterology.

**ACICULAR**

Sharp, needle-pointed.

**ACID-ASH VALUE**

Excess of mineral ions.

**ACID-BASE EQUILIBRIUM**

(1) the relative amounts of anions and cations present in body fluids and the resulting pH; (2) electroneutrality.

**ACID FAST (bacteria)**

Bacteria resisting treatment with acid after staining.

**ACID METAPROTEIN**

A metaprotein soluble in acid and formed when hydrolysis takes place in acid solution (also by pepsin).

**ACID NUMBER**

The number of milligrams of potassium hydroxide needed to neutralize the free fatty acids of 1 gram of a fat, oil, or wax.

**ACIDOSIS**

A condition of lowered alkali reserve with unaltered pH of the blood; a symptom due to excessive acid formation as in surgical anesthesia, gastro-intestinal disturbances, febrile diseases or insulin deficiency; excessive loss of alkali as in cholera or burns; defective acid elimination as in uremia or asphyxia; or excessive ingestion of acid as in drugs.

See Blood, Acid-Base Balance of.

**ACKERMAN REACTION FOR GUANIDINE**

When 3 parts of guanidine are heated with 4 of benzenesulfon-chloride, 6 of 33% sodium hydroxide solution and 30 of water, the cooled reaction mixture yields white needles melting at 212°C.

Reference: Zeit. physiol. Chem. 1906, 366.

**ACOCANTHERIN**

See Ouabain.

**ACOELOMATA**

Animals without a body-cavity, such as sponges.

**ACONITINE**

Acetylbenzoylaconine; potent aconitine; the chief alkaloid of aconitum or monkshood; produces slowing of pulse and fall of pressure; hydrolyzes to benzoic acid, acetic acid and a base, aconine; fatal dose as little as 1/10 grain.

**ACRANIA**

Vertebrates without skulls, such as amphioxus.

**ACREE REACTION FOR PROTEINS**

A violet ring is produced when 0.01 gm. of protein is mixed with 0.1 cc. of 1:5000 formaldehyde and underlaid with 0.5 cc. of concentrated sulfuric acid. See Rosenheim.

Reference: J. Biol. Chem. 2,145 (1906). Am. Chem. J. 37, 604 (1907).

**ACREE-ROSENHEIM REACTION**

A modification of Liebermann's test for proteins. Protein, formaldehyde and concentrated HCl are warmed together, whereupon a violet to blue-black color is produced. The formaldehyde increases the sensitivity of the reaction.

**ACROMEGALY**

The overgrowth in adults of those parts of the skeleton that can grow, the head, the feet and hands, due to excessive production of the growth principle of the anterior pituitary.

**ACROSOME**

The substance of the spermatozoon head.

**ACTINIASTEROL**

A sterol,  $C_{27}H_{44}O$ , containing two double bonds, occurring in the sea anemone, *Anemonia sulcata*.

**ACTINIC RAYS**

Radiations effective chemically, applicable especially to the ultra-violet.

**ACTINIOHEMATIN**

A respiratory catalyst containing haem, but a different protein than hemoglobin, found in certain actiniae.

**ACTINOMYCETALES**

See Microbiology.

**ACTINOMYCETES**

See Cellulose Decomposition.

**ACTION**

(1) The quantity factor of radiant energy; (2) energy multiplied by time.

**ACTION POTENTIAL (CURRENT)**

See Bioelectric Potentials.

**ACTION TIME**

The time interval between stimulus and response; latent period.

**ACTIVATION**

The transformation of biologically or catalytically inactive forms of enzymes, viruses or other catalysts to the active forms.

**ACTIVATOR**

A substance whose presence is necessary for the initiation of activity, e.g. in enzyme reactions.

**ACULEATE**

Having a sting.

**ACYLASE**

A peptidase which hydrolyzes polypeptides with a terminal tyrosine group, postulated for the pancreas by Abderhalden (1930).

**ADAMANTOBLAST**

A cell which forms enamel.

**ADAMKIEWICZ REACTION**

A specific test for tryptophane or indole derivatives; the protein is treated with acetic acid, then stratified over concentrated sulfuric acid. A violet to blue-black ring developing at the juncture of the two liquids is a positive test.

**ADAMKIEWICZ REACTION FOR PROTEINS**

A reddish-violet color and a slight green fluorescence is produced upon the solution of protein substances in glacial acetic acid followed by the addition of concentrated sulfuric acid.

Delicacy of the test is increased by addition of an equal volume of glacial acetic acid to the test solution and floating the mixture on an equal volume of concentrated sulfuric acid. Either free or combined tryptophane is indicated by the reaction.

Reference: Ber. 8,161 (1875). Zeit. anal. Chem. 14, 196 (1875); 15,467 (1876). Hammersten, Arch. ges. Physiol. 36,389. Dakin, J. Biol. Chem. 2,289 (1906). Hopkins, Cole, Proc. Roy. Soc. (London) 68,21. Moltram, Biochem J. 7,249 (1913). Osborne, Harris, J. Am. Chem. Soc. 25,853 (1903).

**ADAMS' METHOD FOR MILK-FAT**

A quantitative method for determining milk-fat by absorption of sample on fat-free paper coil,



drying, followed by extraction with ether. The fat in ether extract is weighed after drying.

# ADAPTATION

A process of adjustment by a living organism to its environment, both living and inert, so as to favor the survival of the organism.

# ADDISON'S DISEASE

Chronic suprarenal insufficiency; a disease characterized by pigmentation of the skin, muscular and nervous asthenia and anemia, due to insufficiency of adrenal (suprarenal) glands, especially of the cortex; asthenia is shown by easy tiring, soft pulse.

# ADELOCODONIC

Pertaining to living forms which form an inseparable colony.

# ADELOMORPHIC

Of indefinite structure.

# ADENASE

An enzyme which deaminates adenine (6-aminopurine) to hypoxanthine (6-oxypurine).

# ADENINE

6-aminopurine; an aminopurine occurring in nucleic acids,  $C_5N_4H_5$ , and combined as adenyly pyrophosphate; of importance in muscular contraction.

See Plant Growth Hormones.

# ADENINE TESTS

See Kossel, Krueger.

# ADENOID

Gland-like; hypertrophied nasal lymphatic tissue.

# ADENOSINE

A nucleoside consisting of one molecule of adenine and one molecule of d-ribose. May be considered as derived from inosinic acid through the loss of phosphoric acid. The linkage is through  $C_1$  of the sugar to an N of the adenine.

# ADENOSINEPOLYPHOSPHATE

See Phosphate Bond Energy.

# ADENOSINETRI-PHOSPHATASE

See Enzymes, Non-Proteolytic.

# ADENYLIC ACID

The nucleotide of adenine, ribose and phosphoric acid.

See Phosphate Bond Energy.

# ADENYLIC ACID SYSTEM

The phosphorylating-dephosphorylating coferment system (adenylic acid, adenosine-diphosphoric acid and adenosine-triphosphoric acid) which with Mg ions is necessary for lactic acid formation and fermentation.

# ADENYLPYROPHOSPHATE

See Creatine and Creatinine Metabolism.

# ADEPS (lard)

The U.S.P. term for the purified internal fat of the hog used in preparation of ointments.

# ADERMIN

See Vitamin B<sub>6</sub>.

# ADHESION

Sticking together due to the contact of dissimilar substances, as glue to wood.

# ADIABATIC

Thermally insulated or self-contained.

# ADIPIC ACID

$C_6H_{10}O_4$ ; m.p. 153°; a dicarboxylic acid present in beet juice.

# ADIPOCELLULOSE

Cellulose containing much suberine; cork tissue.

# ADIPOCERE (Corpse wax)

Waxy material present in corpses removed from watery graves probably consisting largely of insoluble calcium, magnesium and

ammonium soaps of saturated fatty acids. Formerly, it was believed that adipocere originated from protein.

See Steroids.

## ADIPOSE

Fatty; containing fat cells.

## ADLER BENZIDINE TEST FOR BLOOD

A blue color is produced when blood in water is acidified with acetic acid, treated with benzidine solution and hydrogen peroxide.

Reference: Zeit. physiol. Chem. 41, 59 (1904). Einhorn, Deut. med. Wochschr. 1907. 1089. Ascarelli, ibid. 1908, 1089. Walter, ibid. 1909. 130; 1910, 309. Bordas, Compt. rend. 1910, I, 562. Groat, J.A.M.A. 61, 1897 (1913). Wagner, Zent. Chir. 1914, 1182. Lyle, Curtman, Marshall, J. Biol. Chem. 19, 445 (1914).

## ADLER LEUCOMALACHITE GREEN TEST FOR BLOOD

The blood spot is saturated with a solution of pure leucomalachite green (tetramethyldiaminotriphenyl methane). Upon moistening with 3% hydrogen peroxide the spot becomes intensely green.

Reference: Zeit. physiol. Chem. 41, 59 (1904). Schlesinger, Holst. Deut. med. Wochschr. 906, 1444. Michel, Chem.-Ztg. 1911, 471; 1912, 93, 105. v. Furth, Zeit. angew. Chem. 1911, 1625. Medinger, Deut. Zeit. ges. gerichtl. Med. 19, 446 (1832). Fetzner, Nippe, Münch. med. Wochschr. 61, 2093 (1914).

## ADMIRALTY TEST

A test for the efficiency of excremental disinfectants in which gelatin and starch are employed as organic test substances.

## ADONITOL

A pentose sugar found in *Adonis vernalis*.

## ADP

Adenosine - di - phosphate. See Phosphate Bond Energy.

## ADRENAL (Gland)

Suprarenal (gland); a gland above the kidney the cortex of which secretes a hormone regulating sex, fatigue, etc. and the medulla of which secretes adrenalin.

## ADRENAL

Suprarenal; above or near the kidneys.

## ADRENAL CORTEX

### HORMONE EXTRACT (Units)

No official standards. Rat unit is based on the percentage of rats that can be kept alive by the preparation after adrenalectomy. The dog unit depends on the maintenance of a normal nitrogen concentration in the blood. One R.U. = 20-40 dog units.

## ADRENALIN(E)

Epinephrine; suprarenin;  $C_9H_{13}O_3N$ ; a hormone secreted by the adrenal glands serving to increase blood pressure, to strengthen the heart beat and to raise the blood sugar.

## ADRENALINE OXIDASE

See Amine Oxidase.

## ADRENALS

See also Teeth, Biochemistry of.

## ADRENERGIC

Pertaining to nerves that liberate an adrenalin-like substance on stimulation.

## ADRENALONE TEST

See Paget.

## ADRENINE

See Adrenaline.

## ADRENOCORTIN

Natural adrenal cortex hormone extract; cortin.

**ADRENOTROPIC**

(adrenotropic hormone)

A pituitary hormone stimulating the secretion of adrenalin by the medulla of the adrenal gland.

**ADRENOXINE**

An oxidizing substance thought to be formed in the lungs by the combination of oxygen and the internal secretion of the adrenals.

**ADREPHINE**

A mixture of adrenalin and ephedrine; an astringent for the nose, throat and larynx.

**ADRIN**

A commercial preparation of l-epinephrine hydrochloride.

**ADSORPTION**

The phenomenon of concentration at interfaces manifested by substances which decrease interfacial tension, usually, but not necessarily between liquid-liquid or liquid-solid interfaces; manifested in drying solutions over a solid drying agent, or decolorizing and deodorizing with charcoal. Positive adsorption: the concn. of the solute in the interfacial film.

Negative adsorption: the concn. of the solvent in the interfacial film.

**ADSORPTION COMPOUNDS**

Compounds formed at interfaces in heterogeneous systems, not involving primary valence bonds.

**ADVENTITIOUS**

Accidental; arising in unusual positions.

**A.E.**

See Avena Einheit.

**AEROBE**

An organism that must have free oxygen to sustain life.

**AEROBIC**

Referring to bacteria which require oxygen for life.

**AEROBIOSIS**

Living in presence of oxygen only.

**AEROSPHERE**

Atmosphere.

**AEROTAXIS**

Movement of microorganisms with respect to oxygen source.

**AEROTROPISM**

Response to change in oxygen content.

**AESCULETIN**

See Esculetin.

**AESCULIN**

See Esculin.

**AESTHESIA**

Sensation, feeling.

**AESTIVAL**

Pertaining to summer.

**AESTIVATION**

Dormancy of a plant under extremes of dryness.

**AETIOLOGICAL CHEMISTRY**

See Biochemistry (Definitions).

**AETIOLOGY**

The causative development factors leading to a condition, such as a disease.

**AETIOLOGY, CHEMICAL**

See Biochemistry (Definitions).

**AFFECT**

A feeling; an emotion.

**AFFERENT**

Conducting toward the central nervous system or some particular center in it.

**AFFINITY**

Chemical potential; tendency to unite.

**AFTERBIRTH**

Placenta expelled after birth.

**AFTER-POTENTIALS**

See Bioelectrical Potentials.

**AGAMETE**

Cell which fails to unite sexually.

**AGAMIC**

Asexual; parthenogenetic; reproducing without intervention of male.

**AGAMY**

Absence of sex organs.

**AGAR**

See Agar-agar.

**AGAR-AGAR**

The water soluble colloidal carbohydrate of the red seaweed, *Gelidium*; forms gels with as little as 1 part to 500 of water.

**AGARIC ACID**

See Agaricin.

**AGARICIN**

$C_{22}H_{44}O_7$ ,  $1\frac{1}{2} H_2O$ ; agaric acid; lactic acid; a substituted lauryl citric acid, found in a fungus of larch trees; used to control night sweats.

**AGGLOMERATE**

A group of organisms; a collection.

**AGGLUTINATE**

To clump together, as in the case of bacteria, blood cells, etc.

**AGGLUTINATION**

See Immunological Phenomena.

**AGGLUTININ**

Substance which causes clumping of bacteria, bloodcells, spermatozoa, etc.

**AGGLUTININS**

See Immunological Phenomena.

**AGGLUTINOGEN**

Precursor of agglutinin.

See Immunological Phenomena.

**AGGLUTINOGENS AND GENES**

See Genetics, Biochemical.

**AGGRESSIN**

Toxic substances formed by organisms which paralyze the host's defenses. (obsolescent)

**AGLUCONE**

Aglycone; the name given to the group of the non-sugar residues of the glycosides.

**AGLYCONE**

See Aglucone.

**AGMATINE**

$\delta$ -guanidino-butylamine. A poisonous amine formed by bacterial decomposition of arginine; also derived from herring spawn or ergot; lowers blood sugar.

**AGNOSTEROL**

$C_{30}H_{48}O$ ; m.p.  $162^{\circ}C$ . A pentacyclic sterol with 3 double bonds found in lanolin. H. S.

**AGOSTINI TEST FOR GLUCOSE**

Five drops of the test solution are treated with 5 drops of 0.5% gold chloride solution and 2 drops of 1:20 potassium hydroxide solution, heated to boiling and cooled. A violet color indicates glucose; the test is sensitive to 1:10000.

Reference: J. pharm. chim. (5), 14, 464. Rosenfeld, Deut. med. Wochschr. 1888, 451, 479.

**AGRICULTURAL BIOCHEMISTRY**

Agricultural biochemistry is a branch of applied biochemistry which concerns itself with any and all possible situations involving life processes in the pursuit of agriculture. These may include numerous issues such as the cycles of soil organisms, the nurture of plants and their entire metabolic history, animal husbandry from birth to death, pathological conditions to both plants and animals, the biochemical aspects of genetics in the service of breeding, the preparation of animal and plant foods, the control of insects, the processing of farm products, quick ripening, storage, etc.,

from the peculiar viewpoint of agriculture which may be described as the economic utilization of the farm for the production of food. There is also a growing tendency to include the biochemical aspects of chemurgy, which is the utilization of farm products for industrial purposes, such as the production of power alcohol, solvents, drugs, etc.

Where soils and crop improvement are concerned biochemistry is involved in the so-called "classification of soils," their preparation, the working over of fertilizers and their production by the aid of living organisms, and even genetic studies, in which chemicals, e.g. colchicine, are used to produce large or new plants. The effects of heat and cold, chemical reagents like ethylene, on storage and ripening have also biochemical aspects. The ethylene is supposed to react with starch in the ripening process. This field also should include aquaculture, or the growth of plants on synthetic nutrients in solution.

A large division of this subject deals with animal nutrition with the practical objective of obtaining more and better eggs, butter, milk and the like. An agricultural biochemist's interests might lead him to administer female sex hormones in order to induce virgin animals to secrete large amounts of milk. Fertility is an important consideration, and involves the usual attention to vitamin E and the like. Where animals are produced for food the conditions for rapid growth are a subject of serious study. Diets are investigated for special effects, e.g. the kind of fat to develop on a hog.

The pathological aspects of the lives of animals and plants occupy a great deal of the attention of the

biochemist in this field. Plant diseases are of a very great variety and attack selectively seeds, roots, stems or leaves. The toxic agents have been extracted in many cases. The first viruses to be studied were plant disease viruses. An entire subject, "forest pathology," has grown up recently, which can be listed here as a close relative of agricultural biochemistry.

#### AGROSTOLOGY

Division of botany dealing with grasses.

#### AGUE

See Malaria.

#### A+HORMONE

See "A-hormone".

#### A-HORMONE

A substance which influences genetically a number of characters, colors of eyes, testes, skin and brain, of wild-type moths; found in the testes, but not species specific.

#### AIR-BLADDER

The organ of pressure regulation of a fish.

#### AIR-CELLS

Air-filled spaces in bones or lungs.

#### AKROPEPTIDE THEORY

A theory of protein structure advanced by Fodor. Enolization takes place at the peptide linkage of a dipeptide leaving a free valence bond on a carbon and nitrogen atom, which combine with similar bonds on another molecule of the dipeptide yielding a tetrapeptide. This process is repeated, yielding a di-tetrapeptide. By heating proteins with suitable depolymerizing agents, he has been able to isolate tetra-tetrapeptides, di-tetrapeptides and peptides.

**d-ALANINE**

$C_3H_7O_2N$ ,  $\alpha$ -aminopropionic acid; an amino acid of nearly all proteins, crystallizing in small rods, v. sol. hot, sl. sol. cold  $H_2O$ ; m.p.  $270^\circ C$ . I.p. 6.21.

**ALANINE METABOLISM**

Alanine is converted to  $\alpha$ -ketopropionic acid and  $NH_3$ , the latter going to urea and the former probably losing  $CO_2$  to form the next lower fatty acid. Alanine may be converted into glucose. It is thus anti-ketogenic. Under certain conditions it is synthesized in the body.

**ALANINE TESTS**

See Fischer, Komm-Boehringer, Neuberg, Sanchez.

**ALAR**

Winglike.

**ALBÉN REAGENT FOR**

**ALBUMIN IN URINE**

Five gms. of tannic acid are dissolved in a mixture of 240 cc. of 50% acetic acid. A turbidity or precipitate when urine is treated with the reagent indicates albumin.

Reference: Zeit. anal. Chem. 30, 108, (1891). Ott, Verhandl. Kong. Inn. Med. 1895. Tognetti Gazz. Ospedali clin. 1906, 60.

**ALBINISM**

Absence of pigment where it normally occurs.

**ALBINO**

Individual with pigmentary deficiencies of a marked character (in skin, hair, eyes).

**ALBUMEN**

A specific protein, such as white of egg; a general term for a class of proteins.

**ALBUMIN (IN URINE) TESTS**

See Almen, Barral, Exton, Heller, Lugol, Molisch, Pons.

**ALBUMINOIDS**

In the American Classification of proteins—simple proteins having essentially the same chemical structure as the other proteins but highly insoluble in all neutral solvents, and in general, in dilute acids and alkalies; scleroproteins. Examples: keratin, spongin, fibroin and collagen.

**ALBUMINS**

In the American Classification of proteins—a subclass of the simple proteins, crystallizable, soluble in water and salt solutions, and coagulated by heat. E.g. egg, contains carbohydrate groups and should actually be classified with the conjugated proteins.

**ALBUMINURIA**

The older, less accurate but common name for proteinuria.

**ALBUMINURIA,  
PHYSIOLOGICAL**

See Exercise.

**ALBUMOSES**

See Proteoses.

**ALBURNUM**

The soft, sap-wood next to the bark.

**ALCAPTONURIA,  
HEREDITARY**

See Genetics, Biochemical.

**ALCOCK'S THEORY OF  
PROTEIN ANABOLISM**

Amino acids as such do not build up proteins, but are first broken down to simpler structures. The essential amino acids are necessary, not for proteins, but because of some special function they have.

**ALCOHOL**

(1) Ethyl alcohol made by fermentation or synthetically; (2) a class of organic substances char-



acterized by an OH group of very slight acid properties due to union with certain carbon hydrogen radicles.

## ALDEHYDE

The intermediate stage of oxidation of an alcohol to an acid, characterized by the CHO radical.

## ALDEHYDE MUTASE

An enzyme of mammalian liver and kidney which promotes the simultaneous conversion of 2 molecules of acetaldehyde to one of ethyl alcohol and one of acetic acid; also acts on other aldehydes and promotes the oxidation of aldehydes by a number of alpha-ketonic acids.

## ALDEHYDE OXIDES (potato)

An enzyme of potato juice which catalyzes the oxidation of aldehydes by nitrate, methylene blue, etc. but not by molecular oxygen; needs no coenzyme.

## ALDEHYDE TESTS

See Dakin, Schiff Reagent.

## ALDOLASE

See Enzymes, Non-Proteolytic.

## ALDOSE SUGAR

A sugar containing a group which is an aldehyde or is potentially an aldehyde.

## ALDOSE TEST

See Deniges.

## ALEURITIC ACID

$C_{13}H_{20}O_4$ , m.p. 101.5°, an acid extracted from shellac.

## ALEURONE

Albuminoid particles serving as food reserve in plant protoplasm.

## ALEXIN

See Complement.

## ALGAE

Water-weeds.

See Microbiology.

## ALGIN

Na salt of alginic acid, which is a gelatinous substance from sea weeds, probably polymerized mannuronic acid,  $(C_6H_{10}O_7)_n$ .

## ALGOLOGY

The study of sea-weeds.

## ALIMENTARY CANAL

The complex of organs concerned with feeding and digesting, consisting of mouth, pharynx, oesophagus, stomach, duodenum, jejunum, ileum, colon, rectum and anus.

## ALIMENTARY GLYCOSURIA

The presence of glucose in the urine following the ingestion of very large amounts of sugar.

## ALIMENTARY SECRETIONS

Saliva, gastric juice, bile, pancreatic juice, intestinal juices.

## ALIPHATIC

Those carbon compounds characterized by straight, branched, or cyclic carbon chains, and lacking the benzenoid ring structure.

## ALIPHATIC ALCOHOL TEST

See Neuberg.

## ALIPHATIC AMINE OXIDASE

See Amine Oxidase.

## ALIZARIN

$C_{14}H_8O_4$ ; Anthraquinone dye, m.p. 290°, found as a glucoside in madder.

## ALKALI METAPROTEIN

A metaprotein soluble in alkali; formed when protetin is hydrolyzed by alkali or trypsin.

## ALKALINE-ASH VALUE

Excess of mineral cations.

## ALKALINE TIDE

See Urine.

## ALKALI RESERVE

See Blood, Acid-Base Balance of.

## ALKALOID

An organic base in which at least one nitrogen atom forms part of a cyclic system, usually having marked physiologic action. The term is frequently restricted to substances of plant and animal origin.

## ALKALOIDS, ERGOT

See Ergot.

## ALKALOIDS, PHENOLIC, TEST FOR

See Deniges.

## ALKALOSIS

A condition of increased alkali reserve with unaltered pH of the blood; due to excessive loss of acid from the system as carbon dioxide in excessive pulmonary ventilation or HCl of stomach, or excessive administration of alkali in food or drugs.

See Blood, Acid-Base Balance of.

## ALKALOID TESTS

See André, Bertrand, Cole, Lloyd (Reagent).

## ALLANTIASIS

See Botulism.

## ALLANTOICASE

The enzyme which catalyzes the conversion of allantoic acid into urea and glyoxylic acid; found in fishes associated with uricase and allantoinase.

## ALLANTOIN

Glyoxyldiureide,  $C_4H_6O_3N_4$ , m.p.  $235^\circ$ . Oxidation product of uric acid found in urine of lower animals, as end product of purine catabolism, in allantoic fluid, fetal urine and in plants. Used in the treatment of wounds and ulcers as it clears dead tissue and promotes the growth of new cells.

## ALLANTOINASE

An enzyme which catalyzes the formation of allantoic acid from

allantoin; found in fishes with uricase and allantoicase, also in amphibia and echinodermata.

## ALLANTOIS

One of the embryonic membranes found in reptiles, birds and mammals which serve as a temporary and respiratory organ for the developing foetus.

## ALLELOMORPH

A Mendelian character as considered in the light of a contrasting one; one of the two or more genes which "compete" for a particular locus on a chromosome and which influence in different ways the same body characteristics.

## ALLERGEN

A substance inducing allergy.

See Immunological Phenomena.

## ALLERGY

A changed, hostile sensitivity to the ingestion or inoculation of a substance to which there had been a previous exposure.

See Immunological Phenomena.

## ALLOGAMY

Cross-breeding.

## ALLOMETRY

See Heterogony.

## ALLOPELAGIC

Insensitive to cold or heat in the ocean.

## ALLOTROPY

Existence of a substance in different forms possessing a different set of predominantly physical properties.

## ALLOXANTIN

$C_8H_6O_8N_4 \cdot 2H_2O$ ; uroxin; formed in the hydrolysis of the glycoside, convicin, from soya bean.

## ALLUVIAL

Post-glacial.



**ALMÉN TEST FOR BLOOD IN URINE**

Equal volumes of tincture of guaiac and oil of turpentine are shaken until emulsified, the urine is added and presence of blood indicated by precipitation of an intensely blue colored resin. Test is an application of the Van Deen reaction.

Reference: Neues Jahrb. Pharm. 40, 232 (1873). Zeit. anal. Chem. 13, 104 (1874). Weber, Berlin. klin. Wochschr. 1893, 441; Münch. med. Wochschr. 1904, 1198. Csépai. *ibid.* 1910, 311.

**ALOPECIA**

Baldness.

See Hair.

**ALOY-VALDIGUIE REACTION FOR CODEINE & MORPHINE**

The addition of 3-4 drops of reagent to 2 cc. of concentrated sulfuric acid, followed by the addition of the alkaloid or its salt, produces a color within a few minutes. Reagent — One cc. of 0.1% formaldehyde solution added to 100 cc. of 1% uranium acetate solution. Sensitivity — 0.03 mg. Reference: J. pharm. chim. 4, 390 (1926).

**ALTERATIVE**

Promoting the normal healthy functions of the body.

**ALUMINUM TESTS**

See Dubskey-Hrdlička, Hahn.

**ALVAREZ REACTIONS FOR PYRUVIC ACID AND  $\alpha$ -AND  $\beta$ -NAPHTHOLS**

Ten drops of a solution of 0.05 gm. of naphthol in 1 cc. concentrated HCl with 1 drop of pyruvic acid. Alpha naphthol produces a yellow color in the cold, an orange color on warming and no change on dilution with water. Beta

naphthol yields a red to blue color, changing to yellow on dilution with water or alcohol. The naphthols may be used to test for the pyruvic acid.

Reference: Chem. News 91, 209 (1909).

**ALVEOLI**

See Respiration.

**ALVEOLUS**

A small cavity; tooth socket.

**AMANDIN**

A vegetable globulin protein of kernels of plums, peaches, and almonds; m.w. 208,000.

**AMAUROSIS**

Loss of vision not explained by ocular lesions, caused in the same manner as Amblyopia (which see).

**AMBER**

Fossilized plant resin.

**AMBERGRIS**

A cholesterol-like waxy secretion of the sick sperm-whale.

**AMBISEXUAL**

Pertaining to both sexes; ambosexual.

**AMBLYOPIA**

Dimness of vision not explained by ocular lesions or refractive error. It may be due to traumatism, diseases like syphilis, malaria, diabetes, toxic materials such as tobacco, alcohol, quinine, opium, thyroid extract, dinitrophenol, strabismus, intestinal parasites, shell shock (psychic blindness), nyctalopia (night blindness). It may be congenital or acquired, transient or permanent.

**AMBLYSTOMA**

Salamander.

**AMBOCEPTOR**

A specific immune body necessary for the action of complement on a toxin; see lysin.

**AMBOSEXUAL**

See Ambisexual.

**AMBRINE**

A cholesterol-like product found in whale gallstones.

**AMELIFICATION**

Formation of tooth-enamel.

**AMELOBLASTS**

See Teeth, Biochemistry of.

**AMENORRHEA**

Abnormal absence or cessation of menstruation. Primary amenorrhea refers to nonappearance of menstruation at puberty, secondary amenorrhea to the same phenomenon after normal puberty. Anatomical causes sometimes occur as in surgical or X-ray removal or destruction. Otherwise the principal causes are anemia and tuberculosis. Occurrences have been reported in avitaminosis, insanity, shock, exposure, phantom pregnancy, and many other conditions of an endocrine character, as thyroid hyperfunction or subovarianism. The endocrinological type has been treated with some success by the use of the anterior pituitary sex hormone extracts (e.g. antuitrin-S).

**AMICRONS**

In the Siedentopf and Zsigmondy classification of particle size, those particles not visible in the ultra-microscope.

**AMIDASES**

Enzymes that break the linkage between carbon, phosphorus, nitrogen, etc., e.g. as in acid amides.

**AMINE OXIDASE**

Tyramine oxidase; aliphatic amine oxidase; adrenaline oxidase; an enzyme which catalyzes the oxidation of all sorts of amines by molecular oxygen with the formation of peroxide; helps to detoxify amines formed by putrefaction of amino acids; found in the liver.

**AMINE TESTS**

See Whitehorn Reagent.

**AMINO ACID METABOLISM**

See Alcock's theory of protein anabolism and Koop's deamination theory.

**AMINO ACID OXIDASE**

An enzyme isolated from liver, kidney or intestinal mucosa, which oxidizes natural amino acids and the non-physiologically occurring alpha-amino acids with the exception of beta-hydroxyglutamic acid; resolved into a yellow prosthetic group flavin-adenin dinucleotide and a specific protein; maintains a dissociation equilibrium in the oxidized form.

**AMINO ACIDS**

Compounds with an amino and a carboxyl group. Proteins are built up of  $\alpha$ -amino acids connected by peptide linkage. There are about 50 known amino acids. They exist also in the form of internal salts,  $+NH_3RCO_2^-$ , called zwitterions.

**AMINO ACIDS, DETERMINATION OF**

See also Amino Acids, Physiology of.

**AMINO ACIDS, GLUCOGENIC**

See Carbohydrate Metabolism.

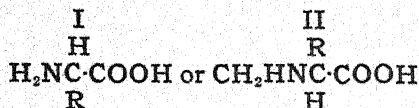
**AMINO ACIDS, KETOGENIC**

See Carbohydrate Metabolism.

# AMINO ACIDS, PHYSIOLOGY OF

Amino Acid Structure of the Proteins. The tissues of our bodies, skin, muscle, tendon, are chiefly protein substances. The number of proteins in the animal and vegetable world appears to be infinite. Yet they are all constructed of about twenty-one units, called the amino acids. These have an extraordinary ability to link together in chains in numbers up to thousands. One definition of infinity might be the possible number of different protein molecules that could be built by permutations and combinations of the amino acids. The extraordinary thing, in fact, is that nature ever succeeds in duplicating a protein molecule. Perhaps she never does exactly. But she comes so close to it that so far as we can tell the casein of cow's milk is always the same, the proteins of muscle seem to be constant in their properties, and so on through the list of proteins that make up the familiar animal and vegetable structures of which we are constructed and on which we live.

The common structure which all the amino acids possess, and which permits this chain-making, may be formulated as:



All the amino acids except proline and hydroxyproline have Structure I, while these two amino acids have II. Each amino acid has an amino group,  $NH_2$  or  $NH-CH_2$ , which has an alkalinity about equal to that of ammonia; and each has a carboxyl group,  $COOH$ , which has the

acidity of an unusually strong organic acid. The R represents a chemical group which is different in each amino acid, and gives it its character as an individual.

In proteins Emil Fischer demonstrated that the amino acids are joined, by what he termed peptide linkings, each  $NH_2$  group condensing with the  $COOH$  of another amino acid, with elimination of the elements of water. Simple chains of a few amino acids, Fischer termed peptides.

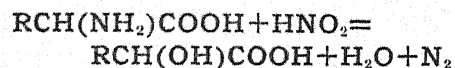
The proteins are peptides of tremendously long chains. These protein chains seem usually to be rolled or folded into balls or otherwise made to take a globular or ellipsoid or sausage shape. Their rates of diffusion were found by Northrop and Anson<sup>1</sup> to approximate the rates that would be calculated for spheres, and the asymmetries calculated from ultra centrifugation are not great. Exceptions are the fibrous proteins, such as silk and wool, in which the molecules appear to be extended into straight wavy chains, long bundles of which make the visible fibres.

Path of Amino Acids through the Body. Except for the transient supply of proteins with which we are born, all those in our bodies are obtained from the proteins of other animals and vegetables, which we eat and digest into their constituent amino acids or simple peptides, and then build into our own tissues. However, only a fraction of the amino acids that we invite into our bodies really find acceptance there as naturalized citizens, integral units of our own structures. Many other fates beset the immigrant amino acid; it may be disintegrated to make some entirely different product; or it may simply be burned for fuel. We

shall try to follow some of the paths in the body that are taken by amino acids after digestion and absorption in the alimentary tract.

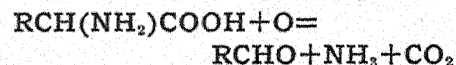
Methods for Determination of Amino Acids. In studies of protein digestion and of the nature and fate of the digestion products, methods for measuring the amounts of amino acids present in blood and other parts of the body are indispensable tools. Two such methods developed in our laboratory have contributed part of the physiological information that will be discussed.

The first was the "nitrous acid method"<sup>2</sup> which depends on the reaction:



The  $\text{N}_2$  gas is a measure of the amount of amino acid present. The reaction is not entirely specific for amino acids, because other amines with  $\text{NH}_2$  groups also react; but such amines are usually not present in important amounts or can be removed.

A later and more specific method<sup>3,4</sup> depends on reaction with a mild oxidizing agent called ninhydrin. Its effect is indicated by the equation:



The analysis consists merely of heating the mixture for a few minutes and measuring the  $\text{CO}_2$  evolved. This reaction is so specific for free amino acids that it serves to pick out and measure them in the most diverse mixtures of other amines, organic acids, peptides and other biological products.

Digestion and Absorption. In the human stomach the chief visible change, as noted a century ago by

Beaumont<sup>5</sup> through the bullet hole in the stomach of Alexis St. Martin, is that food proteins which enter as insoluble matter, such as meat or coagulated egg white, are dissolved. Chemical studies show that the long protein chains are unrolled and broken into relatively short peptide chains, which still, however, are fairly long. No absorption of the products occurs in the stomach; absorption begins only after the chyme enters the intestine.

In the intestine the chyme meets the enzymes secreted by the pancreas and the intestinal wall. These enzymes hydrolyze the long peptides of the chyme to short peptides containing only 2 or 3 amino acids in the molecule, and to free amino acids. Also, any unchanged protein particles that have escaped the gastric juice are digested. The ability of the intestine to digest, not only gastric peptides, but also intact proteins, makes possible the nutrition of people with achylia gastrica and even of persons who have had the stomach completely removed.

Interchange of Amino Acids between Blood and Tissues. Van Slyke, Cullen and McLean<sup>6</sup> found that in dogs during digestion the amino acid content of the blood rose about 20 per cent, as the blood perfused the intestines, and that the greater part of the absorbed amino acids was removed by the liver. In return, the liver poured into the blood of the hepatic vein an amount of urea nitrogen that had been taken up. One could watch the work of the liver in taking up the amino acids and destroying them, turning their nitrogenous parts into urea for excretion by the kidneys. Unreasonable and wasteful though it seems, a large part of the amino acids absorbed

from the intestine appears to be captured and destroyed by the liver, and never to have a chance to reach and nourish the other tissues.

Other experiments, performed with Dr. Gustav Meyer,<sup>7</sup> showed that the liver did not get all the absorbed amino acids, but that some escaped, and could be absorbed by other tissues. It was found that even in the fasting animal the amino acid concentration in the tissues was about 10 times as great as in the blood plasma, viz., about 40 to 60 mg. of amino acid nitrogen per 100 grams of tissue, compared with 5 mg. per 100 grams of plasma. When amino acids were injected into the circulation they were quickly taken from the blood by the tissues, where the amino acid contents might be increased to 2 or 3-fold their former values. In one experiment the amino nitrogen of the liver rose to 150 mg. per 100 grams; in the muscles the increase was never so great. During the next three hours the amino acids in the muscles and kidneys remained practically unchanged, but the amino acids in the liver fell almost back to their original level, and an equivalent of urea nitrogen appeared in the circulation.

**Fate of Amino Acids in the Liver.** The evidence in these experiments, that the liver is the organ where urea formation takes place, supported an old but much contested hypothesis that the liver is the only organ that forms urea. Its unique distinction in this power was confirmed by Bollman, Mann and Magath<sup>8</sup> of the Mayo Clinic, who showed that removal of the livers from dogs led to an accumulation of amino acids in the blood, and entirely stopped the formation of urea.

Another vicissitude of the amino

acids which the work of Mann and his colleagues located in the liver is transformation into glucose. Graham Lusk<sup>9</sup> in the early part of the century showed that when protein was catabolized by dogs made totally diabetic by phloridizin poisoning, about 60 grams of glucose were formed and excreted from each 100 grams of protein catabolized. Lusk and his collaborators also showed that when certain amino acids were fed their carbon was partly or entirely turned into glucose when their nitrogen was turned into urea. Mann<sup>8</sup> and his colleagues showed that no glucose formation from proteins or amino acids occurred when the liver was excluded.

Furthermore, the acceleration of the body's heat production that occurs during assimilation of protein digestion products was shown by Mann<sup>8</sup> and his colleagues not to occur when the liver was excluded. This accelerated heat production, called by Rubner the "specific dynamic action," apparently either represents energy produced by the reactions which the amino acids undergo in the liver, or is caused by other reactions in the cells which are stimulated by the presence of products formed in the liver. Such substances must be other than the urea and glucose, for neither of these causes the observed amount of heat acceleration.

Not all the treatment met by the amino acids in the liver is destructive. During periods of heavy protein feeding the body stores considerable amounts of protein in the liver and, in less amounts per gram of tissue, in the other tissues. The reserve protein seems to be different from the structural proteins of the tissues. In the liver Berg<sup>10</sup> has shown that it can in fact be differ-



entiated with the microscope by its droplet structure in the cells. Functionally it is characterized by the readiness with which it is metabolized at the onset of starvation, and with which it is used to replace blood proteins depleted by hemorrhage, as found by Whipple<sup>11</sup> and his colleagues.

The liver also appears to be the place where plasma fibrin and albumin are formed. It was demonstrated thirty years ago by Whipple<sup>12</sup> that injury of the liver retarded or prevented formation of fibrin. Work by the same author and others<sup>13</sup> has accumulated evidence that the liver is essential also for the formation of the albumin of the plasma. These proteins are presumably formed from free or combined amino acids taken out of the blood by the liver.

**Transamination in the Tissues.** Some of the amino acids can be synthesized in the body. One of the reactions by which the synthesis occurs has recently been discovered by two Russian biochemists, Braunstein and Kritzman.<sup>14</sup> It is called "transamination," and it enables the cells to change keto-acids,  $R \cdot CO \sim COOH$  to amino acids,  $R \cdot CH(NH_2) \cdot COOH$  by replacing the oxygen atom of the ketone CO group with the elements of ammonia. This ammonia, however, must be transferred to the ketone acid from the  $CH(NH_2)$  group of one of the dicarboxylic amino acids, aspartic or glutamic. Since at least some of the keto acids can be produced by partial oxidation of carbohydrates, transamination appears to be one of the processes by which the body can construct a portion of its own amino acids. The reaction of transamination is caused by an enzyme that occurs in all the

tissues, and is rich in the muscles.

**Transmethylation.** The discovery of du Vigneaud<sup>15</sup> that methyl groups can be transferred from methionine,  $CH_3 \cdot S \cdot (CH_2)_2 \cdot COOH$ , to other substances in the body has opened a field rivaling in interest that of transamination. Du Vigneaud proved that choline could be formed with the aid of methyl groups from methionine. He administered methionine in which the methyl of the  $CH_3 \cdot S$  group was marked by hydrogen in the form of deuterium. When this labelled methionine was fed to rats on a choline-free diet choline could be isolated from their tissues with part of its methyl groups containing deuterium. This observation showed that methyl groups had been taken from the methionine to make choline, presumably by methylating ethanolamine. It was found that this marked methyl group could be further transferred from the choline to creatine. The methyl group of the amino acid, methionine, could therefore be used by the body in synthesizing two of its essential non-amino acid constituents, choline and creatine.

**The Continual Replacement of Amino Acids in Living Tissue Proteins.** The extent to which nitrogen fed in the form of amino acids is synthesized into tissue proteins, both in the form of the fed amino acids and of other amino acids formed in the body from the fed material by transamination or other reactions, has been studied brilliantly by Schoenheimer<sup>16</sup> and his colleagues. They have synthesized amino acids with heavy nitrogen,  $N^{15}$ , have fed the amino acids to rats and mice, and have hydrolyzed the proteins in their bodies and isolated various amino acids from

the hydrolysates. Finally, they have analyzed the isolated amino acids for  $N^{15}$  to determine the amounts of the ingested nitrogen that were built into the body proteins, both in the form of the administered amino acid and in the form of other amino acids derived from the administered one by transamination or other processes. They have found that incorporation into tissue proteins began almost immediately, and that, while more of the marked  $N^{15}$  was incorporated in the form of amino acid with which it was administered, than in any other amino acid, nevertheless a considerable proportion of the marked nitrogen was found distributed among other amino acids in the proteins.

The results of Schoenheimer and his colleagues have dispelled the view that the tissue proteins when once laid down remained as unchanging structural blocks until eventually destroyed by the wear and tear of metabolism. It appears that every protein molecule in the living body is itself alive in the sense that it is continually changing and renewing its structure.

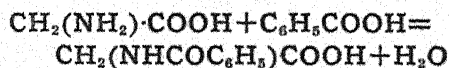
**Essential and Non-essential Amino Acids for Animal Nutrition.** From the fact that by the transaminase action the body can synthesize some of its own amino acids, it would follow that not all the amino acids in the body proteins must be provided readymade in the food proteins, but that some can be made in the body. The task of finding which of the 21 amino acids are indispensable parts of the diet, and which ones the animal body can build for itself, has occupied some of the leading biochemists since the time of Magnus-Levy's<sup>17</sup> demonstration that the rabbit could make glycine. The names of F. Gowland

Hopkins in England and of Lafayette Mendel, T. B. Osborne and W. C. Rose in this country have been especially brilliant in the list of those who have unravelled this problem step by step. As the result of work by all the investigators in the field Rose<sup>18</sup> finally was able to divide the amino acids into the two groups listed in table 1, which must be supplied in the food of growing rats, while the other group can be made by the rat and need not be supplied in the food. The list does not apply to all animals; for example, glycine is indispensable for the chicken. However, it appears probable, although not yet proven, that the necessities of man and the rat are the same or nearly so.

TABLE I

Essential amino acids must be supplied readymade in the diet of rats	Non-essential amino acids need not be supplied in the diet of rats
Lysine	Glycine
Tryptophane	Alanine
Histidine	Serine
Phenylalanine	Norleucine
Leucine	Aspartic acid
Isoleucine	Glutamic acid
Threonine	Proline
Methionine	Hydroxyproline
Valine	Tyrosine
Arginine	Cystine
	Hydroxylysine

**Detoxifying Effects of Amino Acids.** It has long been known that various herbivora and man use glycine to combine with and detoxify benzoic acid by forming hippuric acid:



The synthesis appears to occur in the liver, and the ability to form hippuric acid after glycine feeding is used as a test of liver function.<sup>19</sup>

In some much less obvious way cystine and methionine protect the liver from intoxication by chloro-

form. This peculiar effect of the two sulfur-containing amino acids was discovered by Miller, Ross and Whipple.<sup>20</sup> They had observed that a heavy feeding of meat would protect a dog from the effects of a dose of chloroform that would have led to fatal liver degeneration if administered in the fasting state. Investigation of the different types of amino acids yielded by protein digestion proved that only two containing sulfur had the protective effect.

Nutrition by Intravenously Injected Amino Acids. Henriques and Anderson<sup>21</sup> in Copenhagen demonstrated in 1913 that nitrogen equilibrium could be maintained with intravenously injected amino acids as the sole nitrogen intake. They placed a cannula in the neck vein of a goat kept in a stall, and maintained the animal in nitrogen equilibrium for several weeks by giving the necessary nitrogen in the form of a protein digest hydrolyzed completely to amino acids and injected in a slow stream through the cannula. The therapeutic application did not follow till 25 years later, when Elman<sup>22</sup> began the regular use of intravenous injections of predigested protein. Farr and MacFadyen<sup>23</sup> showed that the injected amino acids were assimilated fully as well as the nitrogen from proteins digested in the alimentary tract. A large part of the nitrogen required can be given in this form for a period of weeks. Whipple<sup>24</sup> and his colleagues and Elman<sup>25</sup> found that when the reserve tissue proteins of dogs had been depleted by fasting and the plasma proteins had also been depleted by bleeding, the proteins could be rapidly restored in tissues and plasma by administering a mixture of amino

acids containing all those essential for nutrition, but not if essential amino acids were omitted. It appears that intravenous amino acid administration can be used to nourish the tissues at times when feeding by mouth is impossible or inadvisable.

Formation of Non-Protein Nitrogenous Constituents of the Body from the Amino Acids. Some of the amino acids in the tissues are condensed into peptides. Of these glutathione, which is glutamyl-cysteinyl-glycine,<sup>26</sup> is active in oxidation-reduction reactions. Carnosine, or beta-alanyl-histidine, occurs in mammalian muscle, and presumably has a physiological function. Another compound of beta-alanine is the vitamin, pantothenic acid.<sup>27, 28</sup> Serine combines with phosphoglycerides to form a constituent of nerve tissue.<sup>29</sup> Furthermore, animals have the power to transform the elements of amino acids in more profound ways than by condensation with their amino or carboxyl groups. Animals can be reared with no other nitrogenous foods than proteins and slight amounts of certain nitrogenous vitamins. Hence it appears that all the nitrogenous constituents that occur in large amounts in the animal organism can be formed from the amino acids yielded by the digestion of proteins. Among such constituents are the purines which form part of the nucleic acids of cell nuclei and the creatine of muscle tissue. The hormones thyroxine and adrenalin, from their organic structures, are presumably derived from tyrosine or phenyl alanine.

## SUMMARY

We have followed the amino acids from their entrance into the



alimentary tract in the form of food proteins through the successive steps of digestion, absorption into the blood stream and passage from the blood stream into the tissues, where they are concentrated by some unknown mechanism to many times their concentration in the blood plasma. We have seen something of the way in which certain of the amino acids can be transformed into one another in the body or synthesized from ammonia and keto acids. However, we have had to admit that our bodies can form in such ways only about half of the different amino acids that are required, and that the other half must be made for us by plants, bacteria or other organisms which have greater synthetic powers than we. And finally we have seen something of the manifold fates of the amino acids after they have entered our tissues; how they may be destroyed and their nitrogenous parts turned into urea in the liver before it is possible to put them to their more specialized uses, how their carbon fractions can be used to form glucose, how they may sacrifice themselves to protect us from toxic products, how they can serve as source material for certain vitamins, hormones and other compounds with physiological functions still to be identified, and how finally those various fates may enter into the proteins of the tissues and become for a time parts of our living structures.

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<sup>1</sup> Reprint from Science, March 13, 1942, Vol. 95, 2463, pages 259-263.

<sup>1</sup> From an address given at the Centennial celebration of the University of Chicago, September, 1941.

<sup>1</sup> J. Northrop and M. L. Anson, Jour. Gen. Physiol., 12: 543, 1928-29.

<sup>2</sup> D. D. Van Slyke, Jour. Biol. Chem., 9: 185, 1911; 12: 275, 1912; 16: 121, 1913; 83: 425, 1929.

<sup>3</sup> D. D. Van Slyke and R. T. Dillon, Compt. rend. lab. Carlsberg, 22: 480, 1938.

<sup>4</sup> D. D. Van Slyke, R. T. Dillon, D. A. MacFayden and P. Hamilton, Jour. Biol. Chem., 141: 627, 1941.

<sup>5</sup> W. Beaumont, "Experiments and Observations on the Gastric Juice and the Physiology of Digestion," 1833. 1929 edition. Boston.

<sup>6</sup> D. D. Van Slyke, Arch. Int. Med., 19: 56, 1917.

<sup>7</sup> D. D. Van Slyke and G. Meyer, Jour. Biol. Chem., 12: 399, 1912, 1912; 16: 187, 197, 213 and 231, 1913.

<sup>8</sup> J. L. Bollman, F. C. Mann and T. B. Magath, Am. Jour. Physiol., 69: 371, 1924.

<sup>9</sup> G. Lusk, "The Elements of the Science of Nutrition," Philadelphia, 1928.

<sup>10</sup> W. Berg, Biochem. Z., 61: 429, 1914.

<sup>11</sup> F. Robschey-Robbins and G. H. Whipple, Am. Jour. Physiol., 112: 27, 1935.

<sup>12</sup> G. H. Whipple and S. H. Hurwitz, Jour. Exp. Med., 13: 136, 1911.

<sup>13</sup> S. C. Madden and G. H. Whipple, Physiol. Rev., 20: 194, 1940.

<sup>14</sup> A. E. Braunstein and M. G. Kritzman, Nature, 140: 503, 1937; Idem, 144: 669, 1939. Also various papers in Biochimia (Russian), 1937 and later.

<sup>15</sup> V. du Vigneaud, M. Cohn, J. P. Chandler, J. H. Schenck and S. Simmonds, Jour. Biol. Chem., 140: 625, 1941.

<sup>16</sup> R. Schoenheimer, Physiol. Rev., 20: 218, 1940.

<sup>17</sup> A. Magnus-Levy, Biochem. Z., 6: 523, 1907.

<sup>18</sup> W. C. Rose, Science, 86: 298, 1937.

<sup>19</sup> A. J. Quick, Arch. Int. Med., 57: 544, 1936.

<sup>20</sup> L. L. Miller, J. F. Ross and G. H. Whipple, Am. Jour. Med. Sci., 200: 739, 1940.

<sup>21</sup> V. Henriques and A. C. Anderson, Z. physiol. Chem., 88: 357, 1913.

<sup>22</sup> R. Elman, Proc. Soc. Exp. Biol. Med., 36: 867, 1937; Ann. Surg., 112: 594, 1940.

<sup>23</sup> L. E. Farr and D. A. MacFadyen, Am. Jour. Dis. Child., 59: 782, 1940.

<sup>24</sup> S. C. Madden, W. A. Noehren, G. H. Waraich and G. J. Whipple, *Jour. Exp. Med.*, 69: 721, 1939.

<sup>25</sup> R. Elman, *Ann. Surg.*, 112: 594, 1940.

<sup>26</sup> F. G. Hopkins, *Biochem. Jour.*, 15: 287, 1921; *Jour. Biol. Chem.*, 84: 269, 1929.

<sup>27</sup> R. J. Williams and R. T. Major, *Science*, 91: 246, 1940.

<sup>28</sup> D. W. Woolley, *Science*, 91: 245, 1940.

<sup>29</sup> J. Folch and H. A. Schneider, *Jour. Biol. Chem.*, 137: 51, 1941; 139: 973, 1941.

## AMINO ACID TESTS

See Abderhalden-Schmidt, Levene-Beatty, Neuberg, Peronnet-Truhaut, Waser.

## AMINO BENZOIC ACID TEST

See Pozzi-Escot.

## AMINOETHANOL

See Choline.

## AMINOETHYLPHOSPHORIC ACID

Occurs in relatively large amounts in malignant tumors.

## AMINOPEPTIDASE

See Aminopolypeptidase.

## AMINOPHORASES

A family of enzymes involved in transaminations e.g. glutamic acid aminophorase, aspartic acid aminophorase; dicarboxylic acids transfer ammonia to mono- and dicarboxylic alpha-ketonic acids, mono-carboxylic acids need the intermediation of some dicarboxylic alpha-ketonic acid; amines and peptides cannot function as ammonia donators and aldehydes, ketones and hydroxy ketones cannot function as acceptors; rates vary for active substances and with source of enzyme, as pigeon muscle.

## AMINOPOLYPEPTIDASE

A group of polypeptide-hydrolyzing enzymes that hydrolyze the polypeptide chain at the amino end.

See Autolysis.

## 6-AMINPURINE

See Adenine.

## AMMONIA TESTS

See Nessler Reagent.

## AMMONIA TOLERANCE TEST

The determination of the amount of urea formed after ingestion of ammonium citrate (diagnostic for liver cirrhosis).

## AMMONITE

An extinct cephalopod.

## AMNESIA

Loss of memory.

## AMNION

The embryonic membrane enclosing the fluid (amniotic fluid) in which bird, mammal and reptile fetuses develop.

## AMNIOTIC

Pertaining to amnion, (fluid, folds, cavity).

## AMOEBIA

Primitive protozoon capable of changing shape by projecting false feet (pseudopodia).

## AMOEBIFORM

Shaped like an amoeba.

## AMOEBOID

Amoeba-like.

## AMORPHOUS

Having no definite (crystalline) form.

## AMPHETAMINE

See Benzedrine.

## AMPHIBIAN

An animal adapted to life both in water and on land, usually starting in the former with gills in the larval or tadpole stage and developing lungs in the adult stage.

## AMPHIGONY

Bisexual reproduction.

## AMPHIMIXIS

The process of blending of heredi-

ty carrying chromatin of the nuclei during cell conjugation in certain protozoa.

**AMPHION**

See Zwitterion.

**AMPHIOXUS**

Lowest vertebrate; lancelet; the probable ancestral marine precursor of all vertebrates.

**AMPHIPNEUST**

An animal using both gills and lungs for breathing.

**AMPHIPYRENIN**

The substance of the nucleus membrane.

**AMPHOLYTE**

A substance capable of giving off or taking on protons; acts as acid toward bases and as base toward acids.

**AMPHOTERIC ION**

See Zwitterion.

**AMPHOTERIC**

A name applied to compounds having both basic and acidic groups, or capable of ionizing both as a base and as an acid.

**AMPLIFICATION, ADAPTIVE**

See Nervous System.

**AMYGDALASE**

See also Enzymes, Non-Proteolytic.

**AMYGDALIN**

$C_6H_5CH(CN)O \cdot C_{12}H_{21}O_{10}$

A glycoside found in the kernels of Rosaceae fruits. It is mandelonitrile amygdalose; crystallizes as rhombs from water, m.p. 200°.

**AMYGDALOSE**

$C_{12}H_{22}O_{11}$ ; the disaccharide composed of 2 molecules of glucose, obtained by hydrolysis of amygdalin.

**AMYLACEOUS**

Starchy; starch-like.

**AMYLASE**

Diastase; enzymes promoting the conversion of starches and glycogens to maltose.  $\alpha$ - and  $\beta$ -amylase convert soluble starch to  $\alpha$ - and  $\beta$ -maltose respectively.

**AMYLASE, ALPHA**

See also Enzymes, Non-Proteolytic.

**AMYLASE, BETA**

See also Enzymes, Non-Proteolytic.

**AMYLASES**

See also Enzymes, Non-Proteolytic.

**AMYLOBIOSE**

A disaccharide obtained by treating polyamyloses formed by Bac. macerans with hydrochloric acid.

**AMYLODEXTRIN**

See Starch, soluble.

**AMYLODEXTRIN**

The first hydrolysis product of starch with amylase; gives purple color with iodine.

**AMYLOGEN**

See Starch, soluble.

**AMYLOID**

Starchy; starch-like.

**AMYLOLYTIC**

Capable of breaking up starch to sugar.

**AMYLON**

The hydrolytic product of potato starch triacetate.

**AMYLOPECTIN**

See Starch.

**AMYLOPLAST**

Starch forming body in plant cell.

**AMYO PROCESS**

A process for making alcohol by the continued action of yeast and a fungus secreting diastase, without the use of malt.

**AMYLOPSIN**

A  $\beta$ -amylase in pancreatic juice.  
See also Enzymes, Non-Proteolytic.

**AMYLOSE**

See Starch.

**AMYLOPHOSPHATASE**

See also Enzymes, Non-Proteolytic.

**AMYLUM**

Latin term for starch.

**AMYTAL**

Isoamyl - ethyl - barbituric acid;  
used as a sedative, hypnotic and  
basal anesthetic; m.p. 153-5°,  
white, odorless, slightly bitter.

**ANABASINE**

The chief alkaloid of *Nicotiana glauca*; oil, b.p. 280-281, 775 mm.;  
Used as an agricultural insecticide.

**ANABOLISM**

Sum of all processes in an organism by which chemical energy in unorganized substances mainly food, is transformed to chemical energy of body substances (build up process).

**ANACIDITY**

See Achlorhydria.

**ANAEMIA**

See Anemia.

**ANAEROBE**

An organism which can live without a gaseous oxygen supply.

**ANAEROBIC**

Referring to the bacteria that do not require oxygen for life.

**ANAESTHESIA**

Loss of sensation; insensibility.

**ANAESTHETIC**

A drug producing anaesthesia.

**ANALGESIA**

Failure to feel pain.

**ANAPHASE**

A stage of mitosis precluding the separation of the chromosomes of each pair.

**ANAPHYLACTOGEN**

See Immunological Phenomena.

**ANAPHYLAXIS**

Allergy; the name given to the protein shock phenomenon shown when a minute amount of foreign protein is injected and a week to a month later another small dose of the same protein is injected. Death frequently occurs a few minutes after the second injection.

**ANASTOMOSIS**

Natural or operative joining of structures, as of nerves or blood vessels.

**$\beta$ -ANATABINE**

$C_{10}H_{12}N_2$  or 2-(3'pyridyl)- $\Delta^4$ -tetrahydropyridine.

An alkaloid of tobacco; Oil, b.p. 145-6°-10 mm.

**ANATOMY**

The study of the structure of organisms as made out by dissection.

**ANATOXINS**

See Toxoids.

**ANCHYLOSIS**

Bony fusion causing stiffness as of tooth to jaw bones, etc.

**ANDRÉ REAGENT FOR ALKALOIDS**

Crystalline precipitates are produced upon the addition of potassium dichromate to many alkaloids — brucine, cocaine, codeine, quinine, etc.

Reference: J. pharm. chim. 1862, 341.

**ANDREASCH REACTION FOR CYSTEINE AND IRON**

The addition of ferric chloride and ammonia to a solution of cysteine

hydrochloride produces a reddish-violet color. The reverse test may be used for iron.

Reference: Jahresber. Tierchem. 76, 1884. Ber. 12, 1390 (1879). Suter, Zeit. physiol. Chem. 20, 562.

## ANDROGEN

A male sex hormone.

## ANDROGENESIS

Egg development via paternal chromosomes only.

## ANDROGENIC

Masculine, masculinizing.

## ANDROGENIC HORMONES

The two male sex hormones, androsterone and testosterone, produced in the interstitial cells of the testis. They control secondary male sex characteristics and accessory sex organs, motility of sperm, composition of semen, and comb growth in the capon.

## ANDROGYNAL

Hermaphrodite, androgynous.

## ANDROGYNE

Hermaphrodite.

## ANDROSE

Male determining substance (hormone, enzyme).

## ANDROSTERONE

$C_{19}H_{30}O_2$ ; m.p. 182-183°C.; a male sex hormone subsidiary to testosterone produced in the interstitial cells. See Androgenic Hormones.

## ANDROSYN

See Digitalis.

## ANEMIA

A deficiency or reduction in the quantity or the quality of the red blood cells; usually measured both by the decrease in the number of red blood cells and the hemoglobin content of the cells; a condition of less than 5 million red cells per cubic mm., while there are 8000 white cells.

## ANEMIAS

Deficiencies in the number of red blood cells and in the hemoglobin content of the blood, which constitute a complex of symptoms, such as pallor, cardiovascular disturbances characteristic of oxygen deprivation, exertion dyspnea and palpitation, tachycardia, arrhythmia, low blood pressure, nervous symptoms, digestive symptoms, menstrual disturbances, loss of libido and albuminuria. The principal types are (1) normocytic (orthochromic) anemias (2) microcytic (hypochromic) anemias and (3) macrocytic (hyperchromic) anemias.

In the normocytic type the number of erythrocytes and the hemoglobin concentration are reduced in strict proportion. It is characteristic of hemorrhage, hemolyses due to poisoning and most infections or it may be "aplastic anemia" due to exhaustion of bone marrow. Blood transfusion is used as emergency treatment. Microcytic anemias are characterized by a reduction of corpuscular hemoglobin below 30% and a decrease of the mean volume of erythrocytes with a color index below one. This is usually caused by iron deficiency, inadequate digestion, exhaustion. The treatment is dietary.

Macrocytic anemias, including "pernicious anemia," have a high color index, with a mean corpuscular hemoglobin content above 30% and a high volume. They are caused by a lack of anti-anemic principle of the liver or the "intrinsic factor" secreted by the stomach. There is often failure of the stomach to secrete free hydrochloric acid. The missing

factors have to be supplied as well as hydrochloric acid.

**ANESTHESIA**

See Anaesthesia.

**ANESTHETICS, LOCAL**

See Pharmacology.

**ANESTRUS**

See Anoestrus.

**ANEURIN**

See Thiamin Chloride; vitamin B<sub>1</sub>.

**ANEURISM**

Arterial abnormal dilatation.

**ANGELIC ACID**

C<sub>5</sub>H<sub>8</sub>O<sub>2</sub>, a monocarboxylic unsaturated acid which occurs in the roots of *Angelica Archangelica*; m.p. 45-46°.

**ANGIOSPERMS**

Flowering plants which produce seeds in ovaries; include monocotyledons and dicotyledons; the monocotyledons include liliaceae, like asparagus, iridaceae like the iris family, crocus gladiolus, the orchidaceae and the grass family; oak, alder are dicotyledons.

**ANGIOTONIN**

An active pressor substance formed from renin and a heat-labile globulin of blood plasma, which itself requires an activator for maximum effect.

**ANGSTRÖM UNIT**

A.U.; one-tenth of a millimicron or one hundred millionth of a centimeter; symbolized Å or A.U.; measure of electromagnetic wave length.

**ANHYDROGITALIN**

See Digitalis.

**ANION**

A negatively charged ion.

**ANION DEFICIT**

See Electrolyte Balance in Muscle.

**ANION IMPERMEABILITY**

See Electrolyte Balance in Muscle.

**ANIONOGENS**

Elements in an unionized state which can become anions in the body.

**ANISOTROPIC**

Having unequal axes.

**ANKYLOSTOMIASIS**

Hookworm disease; uncinariasis; Egyptian chlorosis; a disease due to infection by nematode worms, *ankylostoma duodenale* or *Nector americanus*, attacking the young and undernourished by invasion through the skin. There is a severe dermatitis accompanied by anemia, perverted appetite for dirt, lethargy. Carbon tetrachloride, tetrachlorethylene and thymol are used to drive out the worms.

**ANLAGE**

A region of an embryo destined to develop into some particular organ or structure, as the liver anlage.

**ANNELIDA**

Class of segmented worms; contain (1) polychaeta — ragworm, lugworm (2) oligochaeta — earthworm (3) hirudinea — leaches (4) geophyrea.

**ANODE**

Positive electrode.

**ANODYNE**

A pain-relieving drug.

**ANOESTRUS**

A period of sexual inactivity in animals other than monkeys and men.

**ANOREXIA**

Poor appetite.

**ANOSMIA**

Absence or loss of smell.



**ANSERINE**

Beta-alanylmethyl histidine, a dipeptide isolated in 1929 from goose muscle; m. p. 238°-239°, present in muscles of birds and fishes.

**ANTERIOR**

Nearer to the head; ventral; facing away from axis.

**ANTERIOR PITUITARY HORMONE UNITS**

See prolactin unit, thyrotropic hormone unit, growth factor units, gonadotropic hormone units.

**ANTERIOR PITUITARY-LIKE PRINCIPLE**

Gonadotropic, glycoprotein hormones found in human pregnancy urine (where it is called P.U.), and in pregnant mare serum; forms basis of Aschheim-Zondek test; similar to luteinizing hormone, but formed in the chorionic tissue of the placenta; can cause ovulation, prolongation of pregnancy, diminution of estrogen secretion, but no follicular growth; in the male causes premature descent of the immature testes of primates.

**ANTHOCYANINS (ANTHOCYANS)**

A class of violet, red and blue pigments of fruits, blossoms and leaves of many plants, having the pelargonidin nucleus, which is a substituted benzopyranol nucleus. Some representatives are: delphinidin, pelargonidin, cyanidin, peonidin. Through them inheritance of color in plants may be studied. The pigments attack iron and tin and have caused trouble in canning.

**ANTHOCYANINS AND GENES**

See Genetics, Biochemical.

**ANTHRAX**

Splenic fever; charbon; malignant pustule; woolsorter's disease; a contagious disease caused by *Bacillus anthracis* which may enter through the skin or lungs or sometimes through the intestinal canal. It is found in both animal and human form. Treatment is by antianthrax serum subcutaneously and intravenously if septicemia sets in.

**ANTHROPODESOXYCHOLIC ACID**

Chenodesoxycholic acid.

**ANTHROPOID**

Man or ape.

**ANTIACRODYNIA FACTOR**

See Pyridoxine.

**ANTI-ANEMIC PRINCIPLE**

See Hematopoietic Principle.

**ANTIBERIBERI VITAMIN**

Thiamin Chloride; vitamin B<sub>1</sub>.

**ANTIBODIES**

See Immunological Phenomena.

**ANTICATALASE**

See Catalase.

**ANTICATHODE**

Anode.

**ANTICOAGULIN**

A substance which prevents coagulation of shed blood (as hirudin, snake venom).

**ANTIDROMIC**

Against the normal direction—as a nerve impulse sent peripherally in an afferent nerve.

**ANTI-ENZYME**

(1) old term to designate supposed substance which prevents the splitting of tissues of stomach by its own proteolytic enzymes  
(2) anti-body produced by injection of an enzyme, e.g. antiurease on injection of urease.

**ANTIGENS**

See Immunological Phenomena.

**ANTIGENS AND GENES**

See Genetics, Biochemical.

**ANTIGENS, FORSSMAN**

See Antigens (heterophile).

**ANTIGENS (HETEROPHILE)**

Antigens which evoke antibodies, acting upon biologically unrelated materials, e.g. injection of tissues of various animals leads to the production of sheep hemolysins. The antigens involved in the latter cases are called Forssman antigens.

**ANTI-HORMONES**

Substances which counteract the action of hormones.

**ANTI-KETOGENESIS**

The capacity of certain compounds, notably glucose and glycerol, to prevent the accumulation of acetone bodies by oxidizing them as they are formed. The oxidation of the molecule of glucose facilitates the oxidation of two molecules of fatty acid, the liberated glycerol taking care of the third fatty acid. See ketogenic-antiketogenic balance.

**ANTINEURITIC**

Preventing symptoms of lack of vitamin B, such as polyneuritis.

**ANTINEURITIC VITAMIN**

Thiamin chloride; vitamin B<sub>1</sub>.

**ANTI-PYRETIC**

A substance which lowers the temperature of the body.

**ANTI-PYRINE**

1 - phenyl—2,3 - dimethyl—5 - pyrazolone; an antipyretic and analgesic.

**ANTI-RACHITIC**

Preventing symptoms of lack of vitamin D, such as rickets.

**ANTISCORBUTIC**

Preventing symptoms of lack of vitamin C, such as scurvy.

**ANTISEPSIS**

The prevention of the breeding of microorganisms.

**ANTISEPTIC**

Destructive of pathogenic microorganisms.

**ANTISERA**

See Immunological Phenomena.

**ANTI-THROMBIN**

An active principle of the liver preventing clotting of blood in blood vessels.

**ANTI-TOXIN**

A substance opposed in action to a toxin.

See Immunological Phenomena.

**ANTRUM**

Cavity.

See Gastro-Enterology.

**ANTUITRIN GROWTH FACTOR**

A commercial preparation of anterior pituitary extract.

**ANTUITRIN-S**

A proprietary preparation of chorionic gonadotropin.

**ANUS**

Lower outlet of alimentary canal.

**AORTA**

Principal large artery leading from heart.

**APHASIA**

Loss of speech.

**APHELIOTROPISM**

Turning away from light.

**APHID**

Plant-louse.

**APHONIA**

Inability to make a sound.

**APHOSPHOROSIS**

Phosphorus deficiency.



**APHOTOTAXIS**

Non-susceptibility to light.

**APHRODINE**

See Yohimbine.

**APHRODISIAC**

Substance arousing sex desire.

**APHYLLIDINE**

$C_{15}H_{22}ON_2$ ; an alkaloid of *Anabasis Aphylla*, used as an insecticide; needles, m.p. 112-113°.

**APIGENIN**

See Apiin.

**APIIN**

$C_{27}H_{32}O_{16}$  or  $C_{26}H_{18}O_{14}$ ; a glycoside of the leaves of parsley and celery, consisting of apiose and apigenin; exists as glossy needles of yellow crystalline powder, m.p. 228°C.

**APIOSE**

See Apiin.

**APITUITARISM**

Absence or deficiency of pituitary; hypopituitarism; hypohypophy-sism.

**A.P.L.**

Anterior pituitary-like principle.

**APNOEA**

Stoppage of breathing.

**APOCODEINE**

An alkaloid formed by the dehydration of codein; an expectorant orally and a purgative on injection.

**APOCRINE**

Pertaining to glands; pertaining to part of cell contents (mucus).

**APOCYMARIN**

See Digitalis.

**APOGEOTROPISM**

Negative geotropism.

**APOLEGAMY**

Selective breeding.

**APOMORPHINE**

A synthetic derived from morphine by the action of concentrated acids; has little narcotic action but is a powerful emetic.

**APOPLEXY**

A brain stroke resulting in partial paralysis of speech, motion, etc.

**APOZYMASE**

The name applied to the inactive preparation obtained by the removal of cozymase from zymase, as by dialysis.

**APPENDICITIS**

See Gastro-Enterology.

**APPLE OF PERU**

See Stramonium.

**APPOSITION**

Growth by deposit in successive layers.

**AQUACULTURE**

See Agricultural Biochemistry.

**ARABAN**

A hemicellulose; a pentosan of gum arabic; an anhydride of arabinose.

**ARABINOSE**

An aldopentose, with the hydroxyl group on the opposite side of the carbon chain from the  $\beta$  and  $\alpha$ -hydroxyls; produced as prisms, by boiling gum arabic or beet-root chips with dilute  $H_2SO_4$ . See Eye, Biochemistry of. See also Glycosurias, Non-Diabetic.

**ARACHIC ACID**

See Arachidic Acid.

**ARACHIDIC ACID**

n-Eicosanic acid; a saturated fatty acid,  $CH_3(CH_2)_{18}COOH$  found in peanut oil; m.p. 77°C.

**ARACHIDONIC ACID**

A 20-carbon fatty acid with four double bonds, found in lecithin and cephalin.

**ARACHNIDS**

Arthropods with four pairs of legs, as spiders, scorpions, mites.

**ARAROA**

The source of chrysarobin, a parasiticide, of *Andira araroba*, a Brazilian tree.

**ARBUTIN**

$C_{12}H_{16}O_7 \cdot \frac{1}{2}H_2O$ ; a glycoside of *Arbutis Uva Ursi*, consisting of glucose and hydroquinone; a diuretic and an antiseptic. Crystallizes as needles, m.p. 165°C.

**ARCHAean ERA**

Oldest geologic era of life; includes laurentain period, confined to simple marine invertebrates.

**ARCHEBIOSIS**

Abiogenesis.

**ARCHENCEPHALON**

Primitive fore-brain.

**ARCHETTI TEST FOR**

**CAFFEINE OR URIC ACID**

The substance is added to a nitric acid solution of potassium ferricyanide and heated to boiling; a precipitate of Prussian Blue is obtained if caffeine or uric acid is present.

Reference: *Boll. chim. farm.* 38, 340° (1899).

**ARCHETYPE**

Primitive form or model.

**ARCHIGENESIS**

See Abiogenesis.

**ARCHIPALLIUM**

The primitive mantle or cortex of the cerebrum, primarily concerned with smell.

**AREA OPACA**

Dark outer germinative zone in egg.

**AREA PELLUCIDA**

Light inner germinative zone in egg.

**ARECOLINE**

$C_8H_{13}O_2N$  or methyl ester of 1-methyl tetrahydropyridine carboxylic acid; a parasympathetic stimulating alkaloid of the areca nut; colorless oil, b.p. 209°; large doses cause central paralysis, small doses used as a diaphoretic and anthelmintic.

**AREOLAR**

Spaced as in fibro-elastic tissue.

**ARGENTEUM**

Strong light reflecting area of skin of fishes on sides and belly.

**ARGILLACEOUS**

Clayey.

**ARGINASE**

An enzyme found in mammalian liver and in traces in other organs and tissues, that splits d-arginine into ornithine and urea; is activated by sulphhydryl—heavy metal combinations, particularly cysteine with iron or copper.

**d-ARGININE**

d-guanidine- $\alpha$ -amino valerianic acid; i.p. 10.52, m.p. 238° C.,  $C_6H_{14}O_2N_4$ ; a basic amino acid found in proteins of sperm, seed and other protamines.

**ARGININE METABOLISM**

In mammals and other urea-excreting animals, arginine is converted to ornithine and urea by the enzyme arginase, found chiefly in the liver; synthesized in limited amounts by the body; also a potential source of guanidine acetic acid which can be methylated to form creatine; convertible to glucose in vivo.

**ARGININE TEST**

See Neuberg.

**ARITHMETIC GROWTH**

See Growth.

**ARNICA**

Extract of flowers of *Arnica montana*, used as a remedy for bruises.

**ARNOLD-MENTZEL TEST FOR HYDROGEN PEROXIDE**

When an excess of reagent (1 gm. of vanadic acid in 100 cc. concentrated sulfuric acid) is added to the test solution, a permanent red color is produced. Sensitivity—0.0006%.

Reference: Zeit. Untersuch. Nahr.-u. Genussm. 6, 305.

**ARNOLD TEST FOR ACETOACETIC ACID IN URINE**

Urine is mixed with an equal volume of reagent; the addition of ammonia produces a brownish-red color or precipitate, changing to purple-violet with excess concentrated hydrochloric acid.

Reagent—(1) 1 gm. of p-aminoacetophenone in 2 cc. concentrated hydrochloric acid mixed with 100 cc. of water; (2) 1 gm. of sodium nitrate on 100 cc. of water. In use, mix 2 volumes (1) with one of (2).

Referenc: Wiener klin. Wochschr. 12, 541 (1899). Zentr. inn. 1901, 601. Liplowsky, Zeit. anal. Chem., 40, 565 (1901). Riegler, Münch. med. Wochschr. 1906, 448.

**ARNY-DIMLER TEST FOR LACTIC ACID IN PHARMACEUTICALS**

The substance is extracted with 20 cc. of ethyl acetate; the extract is washed with 5 cc. of water and 5 cc. of dilute sulfuric acid. After filtration through a dry filter paper and evaporation on a steam bath until the solvent is completely evaporated, the residue is dissolved in 5 cc. of 1% resorcinol

solution. Production of a red color when the solution is floated on 5 cc. of concentrated sulfuric acid indicates lactic acid.

Reference: J. Am. Pharm. Assoc. 18, 459 (1929).

**AROMADENDRENE**

The principal sesquiterpene of eucalyptus, b.p. 121° at 10 mm.

**ARRECTORES PILORUM**

Tiny hair erecting muscles in the skin.

**ARRHENOPLASM**

Male plasm.

**ARSENIC TESTS**

See Gutzeit, Marsh.

**ARSENOXIDE**

A compound formed by the oxidation of trivalent As atoms without change of configuration, e.g. as the oxide of arspenamine.

**ARSPHENAMINE**

Salvarsan; arsenobenzene; arsenobenzene dihydrochloride; Ehrlich's benzene dihydrochloride; Ehrlich's 606; used in syphilis and other spirillum affections (relapsing fever, frambesia, malaria).

**ARSPHENAMINE INJURIES, TEST FOR**

See Kahn.

**ARSPHENAMINE TESTS**

See Abelin.

**ARTERIOLE**

A small artery.

**ARTERIOSCLEROSIS**

"Hardening of the arteries"; a chronic disease affecting arterial walls with inflammatory and degenerative changes as thickening, hardening and loss of elasticity. It is generally expected in old age, essential hypertension, bacterial infection, diabetes, gout, lead poisoning and any abnormal cholesterol metabolism. Symp-

toms are present in the brain (dullness, headache, vertigo) the eye, the heart (angina pectoris, coronary disease, arrhythmias), the kidney, and the extremities (obliteration of the pulse) depending on the case. The treatments are directed toward easing symptoms. Iodides and thiocyanates have a rational basis in cases where cholesterol deposition is marked.

#### ARTERY

A blood vessel carrying oxygenated blood from the heart.

#### ARTHAUD-BUTTE REAGENT FOR URIC ACID

The reagent is a solution of 40 gm. Rochelle salt, 20 gm. of sodium thiosulfate and 1.484 gm. of copper sulfate in a liter of water; one cc. precipitates 0.001 gm. of uric acid.

Reference: Compt. rend. soc. biol. 1889, 625.

#### ARTHRITICIN

See Piperazine.

#### ARTHRITIC

(1) pertaining to joints; (2) having arthritis.

#### ARTHRITIS

A chronic disease of the joints involving changes in cartilages, synovial membranes and bone destruction and new bone formation. It may be brought about by general or focal infection combined with predisposing factors of age and lowered resistance. Two principal forms are (1) the atrophic (rheumatoid) form and the hypertrophic (osteoarthritis). The former attacks the young usually with much pain, the latter is accompanied by bony outgrowths. Many types are described as acute rheumatic arthri-

tis, gonorrheal arthritis, septic arthritis, tubercular arthritis (white swelling), gout, syphilitic arthritis, Charcot's joint, fibrositis (muscular rheumatism). Treatments are palliative and stress physiotherapy combined with rest and exercise.

See also Fever Therapy.

#### ARTHROPODA

Include (1) crustacea — crabs, shrimps, lobsters; (2) insecta — insects; (3) arachnida — mites, spiders.

#### ARTHROPODS

Invertebrates with jointed legs and chitinous or calcareous exoskeleton.

#### ARTHUS PHENOMENON

See Immunological Phenomena.

#### ARTIFICIAL SELECTION

Deliberate human breeding of living forms.

#### ASCARIDOL

$C_{10}H_{16}O_2$ , liquid, cyclic organic peroxide, constituting about 60-80% of oil of chenopodium, used as an anthelmintic.

#### ASCHHEIM-ZONDEK TEST

A test for pregnancy depending on swelling and hemorrhage of the ovaries of immature female mice following the subcutaneous injection of urine of pregnant women.

#### ASCITES

Disease of peritoneum marked by accumulation of large amounts of fluid.

#### ASCOMYCETES

See Microbiology.

#### 1-ASCORBIC ACID

Vitamin C; the anti-scurvy vitamin found in certain greens and citrus fruits. It is unstable to heat and oxidation. It crystallizes in rectangular plates, m.p.  $192^{\circ}C$ ;

sol. in water, EtOH, and Me<sub>2</sub>CO, insol. in fat solvents. Lack of the vitamin leads to scurvy, accompanied by hemorrhage and structural changes in the bony tissues. In the body it can set up a redox system, with its oxidation product, dehydroascorbic acid.

#### ASCORBIC ACID TESTS

See Bachstetz-Cavallini, Barac, Bezssonov, Fujita-Iwatake-Miyata, Medes, Pittarelli, Scudi-Ratish, Szent-Györgi, Tauber, Wait Reaction.

#### ASCORBIC OXIDASE

A plant enzyme which specifically catalyzes the oxidation of ascorbic acid by molecular oxygen to dehydroascorbic acid; optimum pH 6; may be a Cu protein; attacks ascorbic acid homologues.

#### ASEBOTIN

See Phlorizin.

#### ASEPTIC

Free of living organisms in any form.

#### ASEXUAL

Without sex or sex organs.

#### ASEXUAL REPRODUCTION

The reproduction of a multicellular organism by the budding off of a group of cells, or of a unicellular organism by spores.

#### ASMACHER REACTION FOR HISTAMINE

Treatment of a solution of a histamine salt with sodium hydroxide, extraction of the free base with hot chloroform and the addition of 0.2 gm. anhydrous copper sulfate gives rise to a dark blue color.

Reference: Biochem. Zeit. 284, 339 (1936).

#### ASPARAGINASE

A specific enzyme, found in bar-

ley, yeast, bacteria and liver, that hydrolyzes amide N from asparagine, giving aspartic acid; optimum pH 8.

#### ASPARAGINE

Aminosuccinamic acid; the acid amide of aspartic acid found in many proteins;  $\text{CONH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$ .

#### ASPARAGOSIN

A fructosan from the tubers of *Asparagus officinalis*.

#### ASPARTASE

An enzyme found in *Bacterium Coli* that splits out ammonia from aspartic acid yielding fumaric acid.

#### 1-ASPARTIC ACID

Amino-succinic acid;  $\text{C}_4\text{H}_7\text{O}_4\text{N}$ ; an acid amino acid present in animal and vegetable proteins largely as asparagine; crystallizes as rhombic prisms, sl. sol. cold,  $\text{H}_2\text{O}$ ; m.p. 251°.

#### ASPARTIC ACID METABOLISM

Probably forms ketosuccinic acid. The body can synthesize it, so its ingestion is not essential to health. Can be 75% converted to glucose in the body.

#### ASPARTIC AMINOPHORASE

A transamination enzyme of animal and plant tissue which promotes the conversion of aspartic acid and pyruvic acid to oxaloacetic acid and alanine and vice versa; also can do the same with hydroxyaspartic acid.

#### ASPERGILLUS NIGER

See Microbiology.

#### ASPHODELIN

A fructosan.

#### ASPHYXIA

Suffocation.

# ASSIMILATION

The conversion of foreign material into living matter in the constructive phase.

# ASTACENE

Astacin, a carotenoid found mainly in Crustacea; its structure is 3,3'-4,4'-tetraketo- $\beta$ - $\beta'$ -carotene;  $C_{33}H_{44}O_4$ ; occurs in combination with protein in the shell and eggs of the lobster, salmon, shrimp, etc.; is also present in the chicken retina and concerned there with color vision.

See Astaxanthin.

# ASTACIN

See Astacene.

# ASTAXANTHIN

An animal xanthophyll found in crustacea and among other invertebrates; is a diketodihydroxy-beta-carotene and oxidizes to a tetraketo-beta-carotene, astacin or astacene; as astaxanthin dipalmitate the prosthetic group of a conjugated protein which is the blue color of lobster shell, and is set free on cooking, producing its own red color.

# ASTHENIA

General weakness and loss of vitality.

# ASTIGMATISM

Blurred vision due to lack of sharpness of focus of light rays on retina.

# ATABRIN

Chinacrin;  $C_{23}H_{31}ON_3$ , m.p. 245-255°, a powerful synthetic antimalarial.

# ATAVISM

A throw-back to remote ancestral form.

# ATAXY

Loss of voluntary control of movements.

# ATEBRIN TEST

See Wats-Ghosh.

# ATELEOSIS

Midjet-like condition.

# ATHEROMA

A damaged or degenerated part of an artery.

# ATHEROSCLEROSIS

The gradual deposition of cholesterol in the arteries, proportional to age.

# ATIOZYMASE

A name applied to zymase free from magnesium, cocarboxylase and cozymase.

# ATMUNGSFERMENT

Respiratory enzyme.

# ATOM

The smallest particle of an element.

# ATOMIC NUMBER

The number of excess nuclear positive charges or the number of planetary electrons of an unionized atom.

# ATOPEN

An allergen; the substance to which an allergic person is sensitive.

# ATOPI

The condition of being sensitive to an atopen (allergen).

# ATP

Adenosine-tri-phosphate.

See Phosphate Bond Energy.

# ATROPHY

Decrease in size and function; emaciation; arrested development.

See Autolysis.

# ATROPHY, MUSCULAR

See Creatine and Creatinine Metabolism.

# ATROPINE

$C_{17}H_{23}O_3N$ ; an alkaloid found only in traces in solanaceous plants, but obtained by racemization of hyoscyamine; elongated prisms from



alcohol, m.p. 118°; causes dilation of the pupil of the eye; hydrolizes to tropine and tropic acid; checks flow of saliva, mucus, and of HCl of the stomach, and relaxes intestinal spasms.

See Toxicology.

### ATROPINE ALKALOIDS

A group found in plants belonging to the potato family, Belladonna, Stramonium, Hyoscyamus, Scopolia, and comprising atropine, hyoscyamine and scopolamine, q.v.; the cations include stimulation of nerve centers and depression of nerve endings.

### ATROPINE BASE TEST

See Gerrard.

### ATROPINESTERASE

See Enzymes, Non-Proteolytic.

### ATROSCINE

See Hyoscine

### ATTRACTION SPHERE

The parts into which a centrosome divides.

### ATWATER-ROSA-BENEDICT RESPIRATION CALORIMETER

An apparatus for measuring animal heat production and  $O_2$ - $CO_2$  exchange simultaneously. It consists of a well-insulated constant temperature chamber surrounded by running water at a definite temperature. The rise in temp. of the water is a measure of the heat produced. The heat loss from evaporation of water is determined by the gain in weight of a concentrated  $H_2SO_4$  absorber. The  $CO_2$  produced is absorbed by soda lime.

### A. U.

See Angström Unit.

### AUCUBIN

$C_{15}H_{24}O_6$ ; glycoside of the common spotted laurel.

### AUDITORY OSSICLES

The 3 small bones-malleus (hammer), incus (anvil) and stapes (stirrup)—which convey vibration from the external ear drum.

### AURICLE

(1) upper chamber of heart; (2) external ear.

### AUSCULTATION

A system of listening to sounds of the organs.

### AUTOANTIBODIES

See Immunological Phenomena.

### AUTOCATALYSIS

A reaction in which a product of the reaction accelerates it.

### AUTOCHTHONOUS

Indigenous; native.

### AUTOCOIDS

Substances which act as chemical messengers in the blood; hormones (stimulating) and chalones (soothing).

### AUTOGAMY

Self-fertilization.

### AUTOGENESIS

Abiogenesis (first phase).

### AUTOINTOXICATION

Poisoning by toxins absorbed from alimentary canal.

### AUTOLYSIS

Autolysis may be defined as the self digestion of tissues, post mortem. Unless otherwise specified the digestion is assumed to be concerned with the proteins of the tissue. In a broader sense it may also refer to changes which occur to any of the components of a tissue, post mortem.

While the softening of meat on standing, without putrefactive changes, must have been common knowledge antedating recorded history, this phenomenon was first



studied scientifically in 1889 by Salkowski<sup>1</sup> He showed that the process was one of protein digestion carried on by enzymes already present in the tissues, and in every way analogous to the digestion of proteins in the gastro intestinal tract. The broader implications of the process were recognized by the pathologist Jacoby who conceived of the mechanism as operating in the living tissues to cause such changes as he observed in the liver in experimental phosphorus poisoning. It was Jacoby who in 1900 gave the phenomenon its name, and who anticipated in his studies much of the subsequent development of the subject.<sup>2</sup> We believe today that the autolytic mechanism is a physiological one, in constant activity, mediating the changes in cell and tissue masses both in the direction of atrophic shrinkage or protein mobilization and in the reverse direction of growth, and hypertrophy.

Most of the studies of autolysis have been made on mammalian tissues post mortem. The factors which initiate the proteolysis, and those which accelerate or inhibit it, have been investigated in great detail. The much more difficult field of demonstrating the reverse or synthetic process and the conditions which favor or control it is still far from being completely solved or understood.

In the following paragraphs we shall attempt to summarize the significant advances which have been made in this field and the methods used to secure the data. There are extensive reviews of the literature available to the student who wishes to pursue the subject in greater detail and no attempt will be made

here to present a complete bibliography.<sup>3,4</sup>

Illustrations. Perhaps the field under discussion can best be understood if a few typical examples of autolysis are first described.

1. When a muscle system is rendered inactive by severing the nerve, or by artificial immobilization (as in placing a broken limb in a cast), the muscle mass shrinks rapidly at first, more and more slowly as the reaction proceeds, until finally a static situation is attained in which the muscle mass remains constant. The curve of weight loss resembles in every respect a digestion curve which approaches an equilibrium.<sup>5</sup> There is good reason to believe that such an equilibrium is attained between the metabolic requirements of the remaining muscle tissue and its supply of blood and lymph. The muscle system may lose as much as 50% of its mass without numerical decrease of cell population and with no significant changes in water or salt content. While muscular strength is diminished, the essential contractile machinery appears to remain intact. This is a typical disuse atrophy and upon removal of the cast and resumption of contractile function the muscle hypertrophies and eventually regains its original mass and strength. In disuse atrophy we see the gross summation of individual cell shrinkages throughout the tissue, and this is essentially a reduction of the cell proteins and protoplasm. With reduction in active cell mass goes reduction in metabolism to the point at which supply and demand and the removal of waste products are again in equilibrium. It is probable that all autolytic phen-

omena are based fundamentally upon blood supply and that shifts in cell mass are the result primarily of shifts in blood supply, or its equivalent.

2. In its migration to the spawning grounds the salmon takes no food. It may travel hundreds of miles upstream to reach its destination. Muscle fat is consumed in making this journey, and in addition as much as thirty per cent of the muscle tissue.<sup>6</sup> This mobilization is accomplished slowly and without loss of function—though obviously with reduction of contractile strength. During this period the gonads are developing and increasing in mass. The amino acids required for gonadal maturation and for fuel can only be derived from the active muscle tissue, and the only known mechanism for such mobilization is the autolytic process which is known to be present and active in the muscles of this fish.

3. During metamorphosis of the tadpole into the adult frog the muscular tail is slowly and completely absorbed. In this case autolysis alone is first involved in the process and is due to decreased blood supply to the tail. Eventually cells die, and the process of removal may very well be intensified by phagocytic invasion. The fact that even the skeletal connective tissue structures are removed, makes it clear that additional agencies are required to explain the process, since these proteins are not digested by the autolytic enzymes themselves. Since the process is slow the number of phagocytes present in a given area need not exceed the normal count.

4. A very striking example of mobilization of structural and stored protein is seen in insects

during pupation. In the larval honey bee investigated by Bishop,<sup>7</sup> the so called "fat body" develops into a large tissue mass. During pupation this undergoes an orderly disintegration. At the same time larval structures are being replaced by those of the fully developed insect—with all the highly specialized equipment required for its new type of life. The whole process takes place in a closed system, since no food is taken and the only exchange with the outside is by respiration. Bishop was able to demonstrate autolysis of the "fat body," and found that its rate increased during pupation.

5. In the pregnant mammal the mammary gland undergoes hypertrophy in preparation for active secretion of milk. At the close of lactation the gland atrophies again to its resting mass. The first phase is under hormonal control which very likely leads to increased blood supply as a primary step toward hypertrophy. The second or atrophic phase is correlated with a decreasing blood supply and may be hastened by pressure due to partial emptying of the gland. The cycle hypertrophy, secretion and atrophy to the resting condition may be repeated many times by the same gland.

6. In starvation the whole organism loses weight as tissue proteins are mobilized. Some tissues like the liver lose protein rapidly; skeletal muscles lose protein more slowly; heart, brain and the respiratory muscles are maintained with only very slight loss. From the metabolic balance sheet it is clear that after the first easily mobilized reserves of carbohydrate and fat have been burned, the tissue proteins are being converted into ami-

no acids and used as fuel, and that the more essential organs are maintained at the expense of less essential. It is not clear in just what ways this protein mobilization is initiated, but the mechanism by which it is accomplished is autolytic. With return to normal conditions the process reverses and the animal regains its lost tissue proteins from the food ingested.

7. In advanced age there is a gradual shrinkage of the whole organism which seems correlated with the slowly decreasing vigor of the circulatory apparatus.

\* \* \*

**Materials and Scope.** Most of the data upon autolysis comes from studies of mammalian tissues — chiefly liver, kidney and spleen. Practically all mammalian structures have however been studied sufficiently to indicate that the mechanism is the same wherever there are active cells. Certain tissues, like mature white fibrous, elastic, cartilaginous and osseous show practically no autolysis. Such material once laid down does not appear to ever digest itself and is permanent unless invaded by phagocytes. Certain types of leucocytes function as digestive cells, and are provided with special digestive enzymes in addition to the autolytic, just as are the stationary digestive cells of the intestinal tract.

In addition to mammalian tissues, quite extensive studies of the other vertebrate phyla indicates an autolytic mechanism identical with that of the mammal. Among the invertebrates the studies of Bishop already cited indicate an autolytic mechanism in insect tissue, not sufficiently studied as yet to be accurately characterized. Chen and Bradley<sup>5</sup>

reported the very slow autolysis of certain molluscan muscles which resembled vertebrate autolysis qualitatively. Further work in this field (about to be published) shows that molluscs, crustaceae and arachnids whose tissues can be isolated and studied separately, have a digestive pattern nearly identical with that of the vertebrates. The only difference thus far disclosed in this preliminary survey lies in a slight shift of the optimum pH for autolysis toward greater acidity. It seems now almost certain that the autolytic mechanism is universally distributed in animal tissues and is at least superficially the same. It is quite as constant a finding as is respiration itself.

In the plant world less is known of the autolytic mechanism and its distribution, though analogous processes are also found in such forms as the yeasts.

**Methods of Study.** In general the methods that have been used are much alike. Fresh tissue is finely divided and suspended in water. Bacterial growth is prevented by some bacteriostatic agent like toluene or merthiolate. The pH is adjusted with buffers or followed as digestion proceeds, since it affects the results very considerably. Activators or inhibitors may be added. Foreign protein may be added as extra substrate. Finally the tissue may be extracted with various solvents and the enzymes separated by fractional precipitation, or by adsorption techniques, which are designed to isolate them in pure form. Such enzymes, more or less purified and separated from the other cell proteins, may then be studied with naturally occurring pure proteins as substrate material,

or with synthetic substrates of known structure designed to discover the specific linkages attacked.

Most of the earlier work was done with either the tissue proteins alone or with such added proteins as casein, fibrin, gelatin and hemoglobin. Gelatin has been much used among the European investigators. Since it is not a native protein, and has been shown by Anson not to be hydrolyzed by his purified cathepsin, the interpretation of the results must be open to serious question. Undenatured hemoglobin has been shown by Anson<sup>9</sup> to be readily cleaved by cathepsin, to be strictly reproducible, and to be insusceptible to cleavage by secondary proteases of the autolytic group. It may be anticipated that the use of purified hemoglobin will make it possible to determine the amount of activity of the autolytic mechanism in various tissues and species. Such a comparative study cannot yet be compiled because the tissue proteins themselves vary greatly in fragility. Thus the keratins are highly resistant to the common proteoclastic enzyme; collagen is digested by pepsin but not by trypsin or cathepsin; elastin is slowly digested by both pepsin and trypsin while its behavior to cathepsin is not known; liver proteins and hemoglobin are readily fragmented. Thus in comparing the over-all autolytic activity of two tissues directly there are several factors which influence the result—the enzyme concentration and activity, and the protein concentration and fragility. Where extractions of the enzyme are resorted to in attempting such an assay, with the use of a known substrate like hemoglobin, the difficulty of assuring a complete extraction is serious. Willstätter showed

that a part of the cathepsin was easily obtained in solution—the “lyo” form—while the rest was firmly bound by insoluble proteins as the “desmo” form. The same difficulty exists in making cathepsin assays with the use of small molecular substrates.

Autolysis is measured by the rate and extent of cleavage. The methods employed are various and not sufficiently standardized so that the results from one laboratory can always be compared with those from another. It is generally agreed that trichloroacetic acid is a convenient precipitant of the native proteins, and at proper final concentration will remove the unchanged protein while allowing even the larger cleavage products to pass through into the filtrate. A final concentration of about 5% has been found satisfactory. As digestion proceeds more soluble nitrogen appears in the filtrates, and the tyrosine color reaction increases in intensity.

The soluble nitrogen is determined by macro- or micro-Kjeldahl techniques, and the data so obtained probably provide the most direct method of measuring proteolysis we have, and are thoroughly reliable.

The color given by phenolic compounds with the Folin-Ciocalteu reagent has also proven satisfactory as a measure of primary cleavage. Although the color developed is not specific for tyrosine, it nevertheless follows very closely the soluble nitrogen curve, and has the advantage of speed. The color may be estimated by colorimeter or by the various types of photoelectric cells available.

The formol titration of free amino groups in the trichloroacetic acid

filtrate—or the equivalent titration in alcohol—has been much used in the past, while the gasometric methods of Van Slyke and changes in conductivity have had a limited use. Inasmuch as these methods measure total protein cleavage, they are not strictly comparable to the previously mentioned methods, and do not represent primary cleavage alone. The determinations are rapid and easily made and are useful in following total cleavage. They have been widely used in the past, particularly in Europe.

Post mortem changes affecting Autolysis. When a tissue has been prepared as rapidly as possible after death of the animal, and sampled and precipitated at once, the trichloroacetic acid filtrate is characterized by: a small but nearly constant amount of nonprecipitable nitrogen; a slight color test for tyrosine; a small amount of amino nitrogen by formol titration or the Van Slyke reaction with nitrous acid; and a nitro-prusside reaction for -SH compounds that varies from a trace to a fairly brilliant color. The figures are quite characteristic of the tissue and are so constant as to indicate an equilibrium between these components and the tissue proteins on the one hand and the blood and lymph on the other.

The reaction of the interior of the living cell lies between 6.8 and 7.2.<sup>10</sup> Immediately after death and mechanical disintegration this reaction changes rapidly, and becomes more acid. Within an hour it may reach 6.2 in the case of liver, and thereafter slowly return toward neutrality.<sup>11</sup> The acids produced in such a digest are  $H_3PO_4$ , carbonic, fatty acids and lactic in the order of their amounts.<sup>12</sup> The production of these acids is evidently not de-

pendent upon autolysis since in breis made alkaline to begin with, these acids may increase as much as 300% over the initial concentration, without any demonstrable cleavage of the proteins. They do however influence very largely the subsequent rate and extent of the digestion of the proteins.

Proteolysis appears to begin at once post mortem, as measured by the appearance of initial cleavage products. If a latent period exists it is a matter of minutes only, during which the acidity is rapidly increasing.

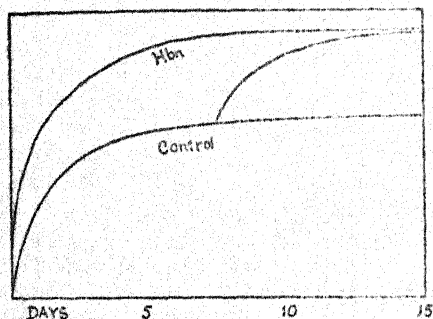
Typical results. After a tissue has been prepared in the cold, to minimize early changes, it is sampled and warmed quickly to the temperature selected for digestion. Samples are removed from time to time and analyzed for soluble nitrogen or tyrosine in the trichloroacetic acid filtrate. Cleavage proceeds rapidly at first, and more slowly later until a stage of digestion is attained at which the reaction ceases, or increases very slowly. This equilibrium point may be reached in three to five days, or may require a much longer period depending on the nature of the tissue. In the case of liver, diluted to a 20% brei, and under the most favorable conditions, digestion of all available tissue proteins is complete in five to ten days. Only the non-digestible stroma proteins remain. In the case of mammalian muscle, about thirty percent of the total protein is digested. When game fish muscle like mackerel is used, a considerably larger fraction of the total protein is digested. The extent of the digestion is characteristic of the tissue. If hemoglobin is added in the late stage, digestion is resumed and continues till the added



hemoglobin is also completely hydrolyzed. Cessation of digestion therefore appears to be determined by the amount of available substrate present in the brei, and under optimum conditions this is digested completely, or very nearly so. Furthermore under the usual experimental conditions for rapid autolysis, cessation is not due to destruction of the enzymes, for these have been shown to survive for many weeks. Cessation of cleavage represents the exhaustion of available substrate.

The following curves illustrate these points. A liver brei at about pH 4.5 is used, with and without added hemoglobin. Digest (1) was set up with hemoglobin added. Digest (2) contained liver alone and served as the control. Digest (3) was exactly like the control, and at the end of ten days hemoglobin was added to it. Resumption of cleavage took place in (3) and attained the same level as in (1).

FIGURE I



The curves illustrate the effect of substrate mass on cleavage products. Digests were maintained at 38 degrees and pH 4.5. Ordinates represent the amount of soluble nitrogen or tyrosine per unit of sample. In liver alone about eighty percent of the total protein was hydrolyzed when digestion became stationary. The rapid digestion of hemoglobin added at this point shows the enzyme to be still active.

In addition to the initial amount of available proteins present in a tissue brei, in determining the amount of cleavage products obtained, two other factors are known which alter the digestion. One is the H ion concentration of the mixture, the other is the oxido-reductive level prevailing. As will be indicated later the H ion concentration affects the mass of available substrate present and also the activity of the enzyme. The oxido-reductive level effects digestion also, but is less well understood. It probably activates the enzyme and it may also activate the substrate.

Effect of H ion concentration. The earlier literature on autolysis described many substances which increase autolysis of a tissue like liver. It eventually became clear that the common factor in all of these accelerators was the production of an acid reaction. (In the case of  $H_2S$  and the colloidal sulphides which slowly hydrolyze to produce  $H_2S$ , there is a second factor present—the -SH effect).

The average pH of a freshly prepared liver brei is usually between 6.5 and 7.0. If the pH is maintained at 7 by means of buffers there is little or no digestion of the proteins. If the H ion concentration is allowed to rise, or is increased by the addition of small increments of acid, digestion is progressively increased and there is less and less undigested material remaining when equilibrium is reached. At pH 4 digestion is maximal, and the only material remaining is the stroma shreds which resist digestion indefinitely. If the H ion concentration is raised beyond pH 4 digestion decreases again and reaches zero in the neighborhood of pH 2.5.



At this level the enzymes are slowly destroyed, and at pH 2 they are destroyed at once.

At pH 7 there is little enzyme activity and no substrate to be attacked. As the H ion concentration rises the enzyme grows more active and the amount of available substrate is increased, as shown by the greater percentage of the total protein hydrolyzed when the reaction has become static. The effect of acid is therefore to increase the actual or susceptible substrate till all that can be made available is thus converted at about pH 4. It is concluded that the acid-protein salt, or the protein cation, is the actual substrate. The base salt, or the protein anion, is not digestible. Certain proteins are rather resistant to cleavage. Egg albumin and the albumin and globulin of serum belong in this group. At a pH greater than 5 these proteins inhibit the digestion of liver itself. At pH 5 they neither increase nor decrease digestion, while at greater acidity they are themselves digested and increase the total cleavage products obtained. The isoelectric points of these proteins are close to pH 5. In more alkaline solutions they are believed to adsorb the enzyme strongly and thus inhibit autolysis, while in reactions more acid than 5 they become fragile and are themselves digested. These results are believed to confirm the hypothesis that it is the acid-protein salt that is the actual substrate material.

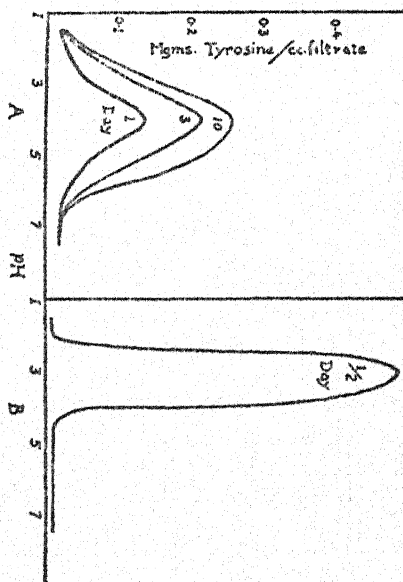
When hemoglobin is added to a liver brei it is digested to some extent between pH 6 and 7. The amount digested increases rapidly between 6 and 4. Since its isoelectric point is about 7 there should be available hemoglobin at all reactions more acid than 7. The rapid in-

crease between 6 and 4, the optimum, lends weight to the idea that the enzyme itself grows more active and reaches its optimum activity in the neighborhood of pH 4.

Since studies with small molecular substrates also show optimum cleavage in this same pH region, we may tentatively conclude that the enzyme itself is most active in this reaction.

In the following figures are shown two examples of the relation of digestion to the pH established in the tissue brei.

FIGURE II



Curve A illustrates the effect of pH on the autolysis of mackerel muscle. It is qualitatively typical of all vertebrate tissue with an optimum pH of 4. Curve B shows the strikingly rapid autolysis of imulus eggs. At the end of twelve hours sixty percent of the available protein was fragmented. In three days digestion was practically complete. The activity range is unusually narrow and the optimum is about pH 3.

It is evident that small changes between pH 7.0 and 4.0 produce very large shifts in the extent of autolysis. While the cell interior probably never reaches a pH 5.0, it is entirely possible that such an acidity may develop at certain areas within the cell at times, and that in such areas the autolytic machinery functions in the direction of hydrolysis with conversion of some protein into diffusible cleavage products which then escape into interstitial fluid, lymph and blood. Atrophies usually develop slowly and involve the loss of only a fraction of the total tissue mass. Where tissues remain constant in mass we may assume that hydrolysis and synthesis are both taking place but are balanced so that no gross change takes place. The concept of a steady state or dynamic equilibrium of this type has had abundant confirmation in recent years through the use of tagged elements. If the areas of higher H ion concentration increase over the areas where active synthesis takes place, to even a slight degree, the cell as a whole will tend to lose protein mass.

Effect of the oxido-reductive level and -SH. This field is under such active investigation at the present time that any generalization must be considered tentative. Certain facts however seem thoroughly established. When a tissue is killed and dispersed, the particles show a nitroprusside reaction for -SH of varying intensity. This reaction normally disappears from the digest within two days. It persists best in the more acid breis. Oxidation to the -SS- form is believed responsible for this change. It is hastened by bubbling air or oxygen through the digest, especially if a trace of

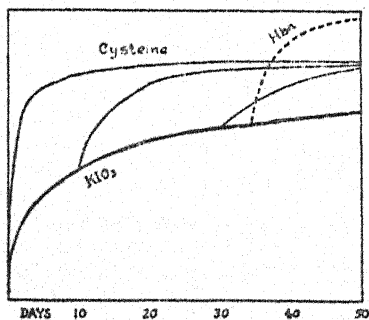
copper salt is present. It may be quickly abolished by adding such oxidants as  $\text{KIO}_3$ ,  $\text{KIO}_4$  or  $\text{I}_2$ . When this is done autolysis proceeds at a greatly reduced rate but eventually attains the same level of digestion as the control. On the other hand, if cysteine or certain other -SH compounds are added to a brei, the digestion rate is usually increased over the control. Where this is not the case it is probable that the -SH reaction is already optimal.

From such data the conclusion has been reached that the oxidative level as indicated by the -SH reaction is an important determinant in the speed with which hydrolysis takes place. When the oxidative level is low and the -SH reaction strong and persistent, autolysis is optimal. There is no clear evidence that the substrate mass has been increased, but the enzyme activity is greater. This is the "activation" effect by -SH first described by Grassmann and Dyckerhoff for yeast<sup>13</sup>, and soon after by Waldschmidt-Leitz et al for spleen.<sup>14</sup> The phenomenon has been studied by a large number of investigators but is still imperfectly understood. The activating effect may be of the enzyme alone, and this is the usual assumption. It is also possible that the substrate is rendered more easily fragmented.

The work of Bergmann, Fruton and their associates<sup>15</sup>, <sup>16</sup> indicates that cathepsin is a complex of proteinases, some of which are activated by -SH and some of which require no such activation. These have been characterized thus far only with synthetic substrates having small molecules. Anson separated a single cathepsin from spleen

which digests hemoglobin without cysteine activation. Bradley et al have presented evidence of two catheptic proteinases in the behavior of whole liver brei.<sup>17</sup> In this study  $KIO_3$  was added to abolish the -SH reaction in a large primary digest. Secondary digests to which cysteine was added were prepared and all maintained at the pH of 4. The enzymes were active at the end of thirty days as was shown by adding hemoglobin without cysteine to a secondary digest set up from the primary digest at that time. The results are shown in Figure 3.

FIGURE III



Digests were maintained at pH 4. The primary digest which was treated with  $KIO_3$  to oxidize -SH compounds, proceeded slowly but showed no indication of leveling off at the end of fifty days. Addition of the fragile protein hemoglobin after thirty four days showed the enzyme to be still active. The addition of cysteine increased the rate of digestion of the available liver proteins.

It will be noted that all cysteine-activated digests reach the same final level. The rapid cleavage of added hemoglobin indicates proteolytic activity at the end of thirty days. Cleavage in the -SH free primary digest was slow but continuous with every indication that in time it would attain the same level as in the activated portions.

The results are intelligible if we assume two proteinase factors present, one of which requires -SH activation, and both of which catalyze the cleavage of the same substrate proteins.

In this and similar experiments in which the whole tissue is used, it is not clear whether cysteine is itself required in the activation of the autolytic process or whether it is merely the indicator of a reducing level which is essential. Ascorbic acid also increases the rate of autolysis, and tends to maintain the sulphur equilibrium predominantly in the -SH form. Bergmann<sup>10</sup> presents evidence that the various activators alter the specificity of the enzyme and so function as co-enzymes. He also shows that the cleavage products influence the specificity of the enzymes, and function as "co-substrates."

Where the tissue digests are maintained at given pH levels, it is found that -SH activation is greatest where the pH is also optimum for autolysis. At pH 7 where digestion is least, there is little activation; at pH 4 activation by -SH is most pronounced. It is clear therefore that the two factors, pH and -SH (or the oxido-reductive potential) are correlated and reinforce each other. Thus in partial asphyxia due primarily to decreased blood supply, the cell will tend to accumulate acid metabolites which activate the enzyme and increase available substrate. Under the same conditions the normal oxidative level is decreased, the proportion of -SH to -SS- increased, the enzyme complex becomes more active and the digestion is accelerated. Equilibrium between synthesis and hydrolysis is disturbed in the

sense of more hydrolysis; the individual cells decrease in mass and as a result the tissue as a whole shows atrophy. The process continues until the metabolism of the diminishing tissue mass is again in equilibrium with the blood and oxygen supply. With return to the original blood supply the new equilibrium is again disturbed, in favor of synthesis; the cells and the tissue hypertrophy to the original mass and metabolic rate.

The above statement is evidently an attempt to correlate what is known of the autolytic mechanism with what is observed in atrophy and hypertrophy. New facts will undoubtedly require its revision. However, it is generally accepted that in some such way this widely distributed enzyme system functions to relate cell mass and tissue mass and their metabolic requirements, to the systems of supply. Its significance lies in the evidence that it functions at all times in maintaining the dynamic equilibria of the living organism, while its post mortem function is only incidental in initiating the removal of dead cells.

When shifts occur in the fundamental factors of supply and demand, the resulting shifts of tissue mass will be permanent or temporary depending upon these fundamental factors. Thus the shrunken muscles of poliomyelitis, of old age or of the tadpole's tail are evidence of permanent changes in the factor of supply. Disuse atrophies of immobilized muscles, the atrophy of the mammary gland as lactation is concluded, or the tissue losses incident to undernutrition are examples of temporary shifts in the supply-demand equilibrium. The growth of tumors or of the body as a whole

are examples of more permanent shifts in the direction of synthesis.

The determining factor in all these changes appears to be the blood supply. Data to support this statement are far from adequate, and there may be other factors equally important. It is obvious however that a cell population situated along a given vascular system and in equilibrium with it, cannot maintain itself unaltered if that blood supply is decreased. Furthermore metabolism is known to be correlated more or less directly with tissue mass, which may imply that cells cannot reduce metabolism except by a decrease of active protoplasm. Thus the shrinkage of the individual units of the population will be the first effect automatically produced by the autolytic mechanism. If the decrease of the blood supply is too great or too prolonged some of the less favorably situated cell units will die, and the population will be numerically decreased. These cells are then removed by their own digestive enzymes and probably also by the intervention of phagocytic cells with their additional specialized enzymes. Both types of atrophy are well known.

**The Autolytic Enzymes.** The tissue proteinases were classified by Waldschmidt-Leitz as consisting of cathepsin, carboxypolypeptidase, aminopolypeptidase and dipeptidase.<sup>18</sup> The last three named make up together the "erepsin" of Cohnheim and were found to be widely distributed in tissues first by Vernon.<sup>19</sup> Cathepsin was believed to be a single proteinase, acting best at pH 4, activated by -SH and similar reducing agents and initiating cleavage of the native proteins of the tissue. The remaining pepti-

dases were believed to act specifically on the polypeptide fragments of primary cleavage, and on dipeptides, with the production of amino acids. The reaction curves of the members of this group overlap sufficiently so that they could conceivably function together in the complete conversion of tissue proteins to their final cleavage units.

The classification above has recently been shown to be inadequate, as has been indicated in previous paragraphs. Based upon separations and studies of specific behavior with synthetic substrates, Bergmann, Fruton and their associates<sup>15, 16</sup> Johnson and Berger,<sup>20</sup> and others have shown that there are probably many more enzymes in tissues than those described by Waldschmidt-Leitz, and that they will eventually be susceptible to an entirely different classification based upon more fundamental characteristics than were disclosed by the earlier work. At the present time it would perhaps be premature to do more than indicate that such detailed studies are in process. The reader is referred to articles which have recently appeared in *Advances in Enzymology* for summaries of this work.<sup>15, 16, 20</sup>

**Protein Synthesis.** Substrate hydrolysis has been the usual criterion of autolytic activity. On theoretical grounds we assume the reaction to be reversible and under proper conditions to lead to the synthesis of protein molecules from cleavage products. The experimental evidence for such reversals is obviously extraordinarily difficult to obtain in a tissue brei. Without the organization of the cell to protect and insure stability of a peptide chain once formed in order that it may

go on to the next step in synthetic growth, the possibility of building up a native protein molecule seems remote. Voegtlin, Maver and Johnson<sup>21</sup> have reported success in such an experiment however, where the environment of the tissue extract, glutathione and cleavage products was changed from anaerobic to aerobic conditions. There have been a few other reports of similar successful syntheses. There have also been failures reported. Perhaps the most convincing demonstration of synthesis was reported by Behrens and Bergmann<sup>22</sup> who showed that liver or spleen cathepsin can catalyze the synthesis of a single specific peptide bond by the use of a well defined simple substrate. This experiment we believe finally completes the evidence which establishes the validity of the major concepts of the autolytic mechanism as functional in both atrophic and hypertrophic tissue changes.

\* \* \*

**Conclusion.** In concluding this account of the autolytic mechanism and its functions, it is suggested that we are dealing here with the most fundamental and primitive proteolytic system, present in all animal cells—perhaps in all cells. In unicellular organisms it functions as the digestive system for converting food proteins into amino acids, and also presumably as the hydrolytic-synthetic system for maintenance of its own cell proteins. Some of these roving unicellular units form part of the "tissues" of highly complex forms such as the lamellibranchs. To secure protein food and to convert it into amino acids for the use of the fixed tissue cells, is the special function of these phagocytes. There is no secretion of proteolytic enzymes into the intestinal

tract for this purpose.<sup>23</sup> These cells wander into the lumen of the gut, engulf particulate material which has been sorted and swept in by the palps and cilia, and wander out again to all parts of the body. Their digestive equipment is limited to this fundamental group of autolytic enzymes.

In higher forms, like the mammal, we find similar mobile tissue cells whose function has become narrowed to the removal of dead and foreign protein material such as bacteria. In addition to the autolytic enzymes some types of these phagocytes have additional proteolytic equipment which increases their effectiveness. Their function in securing and preparing food is evidently secondary to their function in preventing invasion and in clearing away protein debris. In these higher organisms the function of securing food has been taken over by fixed tissue cells which secrete specialized proteolytic enzymes into the gastro-intestinal tract. They retain however the fundamental autolytic complex which maintains their structural integrity and their mass. All other tissue cells, with whatever specialized structure and function, are equipped with this same fundamental mechanism for the maintenance or adjustment of the cell mass to the systems of supply.

The factual basis for this generalization is admittedly incomplete. The systematic study of the invertebrate field has only recently begun. It is anticipated that data in this field will rapidly accumulate to confirm or disprove the validity of the concept. With the exception of the yeasts and some molds, little or no studies have been made of

plant autolysis. In addition therefore to the studies of the specific enzymes, their characterization and quantitative distribution, it may be anticipated that work in the near future will be extended to include these unexplored fields.

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# BIBLIOGRAPHY

- <sup>1</sup> Salkowski, E., *Zeitschr. physiol. Chem.*, 13: 506, 1889; 31: 305, 1900; 34: 158, 1901.
- <sup>2</sup> Jacoby, M., *Zeitschr. physiol. Chem.*, 30: 149, 174, 1900; 33: 126, 1901.
- <sup>3</sup> Jacoby, M., *Beitr. Chem. Physiol.*, 3: 446, 1902-3.
- <sup>4</sup> Bradley, H. C., *Physiol. Rev.*, 2: 415, 1922; 18: 173, 1938.
- <sup>5</sup> Pozzi, L. R., *Accad. Ital. (Mem. Classe Sci. Fis.)*, 6(1): 193, 1935.
- <sup>6</sup> Chen, K. K., Meek, W. and H. C. Bradley, *J. Biol. Chem.*, 61: 807, 1924.
- <sup>7</sup> Greene, C. W., *Am. J. Physiol.*, 29: 39, 1912.
- <sup>8</sup> Bishop, G. H., *J. Biol. Chem.*, 58: 567, 1923-24.
- <sup>9</sup> Chen, K. K. and H. C. Bradley, *J. Biol. Chem.*, 59: 151, 1932.
- <sup>10</sup> Anson, M. L., *J. Gen. Physiol.*, 20: 565, 1937.
- <sup>11</sup> Chambers, R. and T. Kerr, *J. Cell. Comp. Physiol.*, 2: 105, 1932.
- <sup>12</sup> Sevringhaus, E. L., Koehler, A. E. and H. C. Bradley, *J. Biol. Chem.*, 57: 163, 1923.
- <sup>13</sup> Sevringhaus, E., *J. Biol. Chem.*, 57: 181, 191, 1923.
- <sup>14</sup> Grassmann, W. and H. Dyckerhoff, *Zeitschr. Physiol. Chem.*, 179: 41, 1928.
- <sup>15</sup> Waldschmidt-Leitz, E., Purr, A. and A. K. Balls, *Naturwiss.*, 18: 644, 1930.
- <sup>16</sup> Bergmann, M. and J. S. Fruton, *Advances in Enzymol.*, 1: 63, 1941.
- <sup>17</sup> Bergmann, M., *Advances in Enzymol.*, 2: 49, 1942.
- <sup>18</sup> Bailey, B., Belfer, S., Eder, H. and H. C. Bradley, *J. Biol. Chem.*, 143: 721, 1942.



<sup>18</sup> Waldschmidt-Leitz, E. and A. Schaffner, *Zeitschr. physiol. Chem.*, 188: 17, 1930.

<sup>19</sup> Vernon, H. M., *J. Physiol.*, 33: 81, 1905.

<sup>20</sup> Johnson, M. J. and J. Berger, *Advances in Enzymol.*, 2: 69, 1942.

<sup>21</sup> Voegtlin, C., Maver, M. E. and J. M. Johnson, *J. Pharmacol. Exper. Therap.*, 48: 241, 1933.

<sup>22</sup> Behrens, O. K. and M. Bergmann, *J. Biol. Chem.*, 129: 587, 1939.

<sup>23</sup> Yonge, C. M., *J. Marine Biol. Assoc.*, 14 N.S.: 295, 1926-27.

## AUTONOMIC NERVOUS SYSTEM

The part of the nervous system dealing with involuntary actions; A semi independent group of nerve cells and fibers distributed throughout the body and controlling the viscera.

## AUTOPHAGY

(1) Nutrition of the organism on tissue reserves as in fasting; (2) consumption of one's own flesh in insanity.

## AUTOPHYTE

A plant deriving its food from inorganic sources.

## AUTOTOMY

Self-mutilation as in shedding of claws, tails, etc.

## AUTOTROPHIC BACTERIA

See Microbiology.

## AUXENOLONIC ACID

See Plant Growth Hormones, Growth.

## AUXENTRIOLIC ACID

See Auxin-a.

## AUXETICS

Chemical agents inducing cell division.

## AUXIMONE

Accessory growth-promoting factor in plant food.

## AUXIN a

See Plant Growth Hormones.

## AUXIN b

See Plant Growth Hormones.

## AUXINS

See Plant Growth Hormones.

## AUXOCHROME

A group which when introduced into an organic compound containing a chromophor, converts the compound into a dye.

## AVENA EINHEIT

A measure of the potency of the of the plant hormones defined as "that amount of substance which when present in a block of 3% agar-agar, 2mm. x 2mm. x 0.5mm., and applied to one side of a decapitated Avena Coleoptile, will cause a curvature in the coleoptile of 10° in two hours, when kept at 22-23°C and 92% relative humidity."

## AVERTIN

A proprietary name for tribromethyl alcohol, a basal anesthetic; given rectally to produce deep sleep, not permitting operation without the addition of an inhalation anesthetic.

## AVIDALBUMIN

See Biotin.

## AVIDIN

See Biotin.

## AVITAMINOSIS

Diseased condition due to vitamin-deficiency.

## AVITAMINOSIS B<sub>1</sub>

See Beriberi.

## AVITAMINOSIS C

See Scurvy.

See Nervous System.

## AXEROPHTHOL

See Vitamin A<sub>1</sub>.

## AXILLA

Armpit.

**AXOLOTL**

Aquatic American salamander.

**AXON**

Main elongated outgrowth of a nerve cell, which carries impulses from the cell body.

**AZAFRIN**

$C_{27}H_{38}O_4$ ; m.p.  $212^{\circ}$ ; the pigment of the Azafranillo root.

**AZOLESTERASES**

See Enzymes, Non-Proteolytic.

**AZOTOBACTER**

A group of aerobic bacteria found in soils and in water basins and capable of fixing atmospheric nitrogen, under aerobic conditions and in non-symbiotic state; mechanism of fixation believed to be through the ammonia stage, although still disputed; an enzyme,

designated as azohydase is claimed to bring about the reaction of fixation.

**AZOTOBACTER  
CHROOCOCCUM**

See Microbiology.

**AZZOLINI TEST FOR  
EPINEPHRINE  
(ADRENALINE)**

4-5 cc. of test solution are shaken with 1-2 drops of hydrochloric acid and 2-3 cc. of a mixture of 4 parts ammonia and 95 parts alcohol are superimposed. Presence of epinephrine indicated by rose-red ring at alcohol-acid interface. Metallo-organic salts do not interfere. Sensitivity—1:500000.

Reference: Boll. chim.-farm. 70, 665 (1931).

## B

### BABCOCK'S TEST

A test for fat in milk.

### BABO REACTION FOR URIC ACID

Red precipitate of cuprous oxide is obtained when an alkali urate is boiled with dilute Fehling's solution. A white precipitate of cuprous urate is obtained with free uric acid, being converted to cuprous oxide on boiling with alkali.

### BACILLUS

Rod-shaped bacterium which multiplies by division.

See Microbiology.

### BACHSTEZ-CAVALLINI REACTION TO DIFFERENTIATE ASCORBIC AND ISOASCORBIC ACIDS

Addition of 2 drops of 10% uranium acetate solution to a faintly alkaline 1% solution of ascorbic acid produces a slight brown color which is discharged by the addition of a few drops of concentrated sodium hydroxide, followed by precipitation of amorphous sodium uranate. A deep brownish-red color and a clear solution is obtained with isoascorbic acid.

Reference: Zeit. physiol. Chem. 228, 25 (1934).

### BACTEREMIA

See Bacteriophage.

### BACTERIA, CELLULOSE

See Cellulose Decomposition.

### BACTERIA, LUMINOUS

See Bioluminescence.

### BACTERIA, PHOTOSYNTHETIC

See Photosynthesis.

### BACTERICIDIN

A substance which kills bacteria without lysis.

### BACTERIOCHLOROPHYLL

See Photosynthesis.

### BACTERIOLOGY

See Microbiology.

### BACTERIOLYSIN

Substance that destroys bacteria by dissolving them; bacteriophage.

### BACTERIOPHAGE\*

By definition "bacteriophage" (or phage) connotes a large group of sub-microscopic agents which induce transmissible lysis of bacteria and are capable of passing bacteria-retaining filters. They are widely distributed in nature, abound particularly in the intestinal tracts of man and animals and possess particulate diameters within the limits of 8  $\mu$  to 100  $\mu$ . Like the mosaic viruses, purified phage preparations have been found to be nucleoproteins. Molecular weight determinations by means of centrifugation analysis and diffusion have given figures of 400,000 to 300,000,000.

The first observations on bacterio-

phage were made in 1915 by Twort. He noted in colonies of *Staphylococci* isolated from calf-lymph curious, glassy-looking areas within which there were masses of granular debris. He found that it was possible to form vitreous zones in normal cultures by the simple expedient of placing on the surface of a young agar culture a drop of filtrate from a suspension of bacterial growth in which this degenerative change already had taken place.

In 1917 d'Herelle called attention to the same phenomenon observed while he was studying cultures of dysentery bacilli recently isolated from the stools of patients suffering from bacillary dysentery. For no apparent reason ordinary turbid broth cultures of dysentery bacilli would suddenly become crystal clear and this spectacular lysis could be induced in a fresh culture of dysentery bacilli by adding a drop of the filtered, cleared culture. d'Herelle coined the term "bacteriophagy" to denote all phases of the reaction between bacteriophage and the susceptible bacterial host and for several years he studied the phenomenon intensively. He developed the view that phage is a single living organism, "Protobios bacteriophagum" which may adapt itself to live upon a wide variety of bacterial substrates. Others, notably Bordet, believed that phage is a bacterial enzyme of unspecified origin but possessing such properties that its introduction into the bacterial cell disturbs the normal metabolic processes with the result that the cell initiates production of the same agent. The essential difference between the two hypotheses is simply that in d'Herelle's view phages are small living units

stemming from a single parent "race" and acquiring special characteristics by adaptation while Bordet and his followers believe they are modified bacterial proteins. The consensus of opinion among modern workers is that phages are bacterial viruses, protein in nature and altogether analagous to the animal and plant viruses.

## METHODOLOGY

### 1. Isolation of phage

Because phages are so ubiquitous their isolation is not especially difficult and the fact that they are commonly found in the intestinal contents makes crude sewage a good source material. The sewage sample mixed with broth is incubated at 30° C. to 37° C. overnight and then is filtered successively through a small amount of infusorial earth to remove solid debris and a Chamberland L-3 candle or some similar device to retain bacteria. One ml. aliquots of the filtrates are added to 10 ml. amounts of broth in test tubes and each tube is inoculated with sufficient amount of a young culture of the test organism to produce faint turbidity. The test tubes are held at 30° C. for 24 hours and are examined at intervals for clearing. Clearing indicates the presence of an active phage and the cleared culture, after filtering to remove any viable bacteria, may be set aside as a source of phage for the organism in question.

If instead of complete lysis, the test suspensions show only a demonstrable reduction in turbidity they are filtered through L-3 candles and the process repeated with the filtrate. At the same time 1 ml. of the filtrate should be added to 10 ml. of a faintly turbid sus-

pension of the bacteria and 0.05 ml. of the mixture spread over the surface of an agar plate. After incubation the bacterial growth on the agar plate may reveal punched out areas, the 'taches vierges', or plaques, which represent loci of phage action on the bacteria. Microscopic examination will reveal that these plaques contain mostly granular debris resulting from cellular disintegration. Such a plaque may be used as the source material for inoculation of a young broth culture seeded into broth. If this first passage on a broth culture does not produce complete lysis, filtration and serial passage upon the susceptible bacteria should be resorted to.

Since in nature phages commonly occur as mixtures it is desirable to derive 'pure line strains' before undertaking any systematic work. This is accomplished conveniently by spreading the mixed phage, suitably diluted, over an agar surface inoculated with the test organism. After 24 to 48 hours incubation an isolated plaque is selected and the surface is touched with a sterile needle. The minute amount of adherent phage obtained in this fashion is used to induce lysis in a young broth culture. When lysis has occurred the culture is filtered and the filtrate again is plated out for single plaque selection. This repetition is not always necessary although it helps to ensure the isolation of a pure line strain.

## 2. Quantitative methods

Two general procedures for the quantitative determination of phage have been developed. These are: (a) the plaque count and (b) the activity-titration.

(a) The plaque count. The theory of this method is identical with that of the colony count for esti-

mating numbers of viable bacteria. Serial dilutions of a phage-containing solution are plated out on a substrate of susceptible bacteria and the plaques are counted after a suitable period of incubation. Since each plaque is assumed to be the locus of action of a single phage molecule, the plate count multiplied by the dilution factor gives the number of phage particles in the original solution.

Gratia has evolved a superior method of performing the plaque count. In this procedure the essential steps are:

- (1) Add 0.5 ml. aliquots of phage dilutions to 3.5 ml. amounts of a broth suspension of bacteria containing  $1.6 \times 10^8$  organisms/ml.
- (2) Mix thoroughly and quickly with 1 ml. portions of 2.0% agar heated to 100° C.
- (3) Remove 1 ml. to the surface of a previously poured and solidified 2% extract agar plate and smear over the surface with a sterile 15 mm. loop.
- (4) Incubate and count the plaques.

(b) The activity titration: The Krueger activity assay depends upon the fact that the time at which lysis occurs in a standard suspension of susceptible bacteria maintained under certain controlled conditions is a function of the amount of phage present at the start of the reaction. The quantitative activity unit employed has the dimensions of a velocity constant and in the case of the *Staphylococcus* and anti-staphylococcus phage studied by Krueger and his co-workers there are about  $1 \times 10^{10}$  such units in each ml. of ordinary lysate. This

corresponds to about 1/3 plaque per activity unit.

To conduct a phage activity assay with the *Staphylococcus* and anti-staphylococcus phage mentioned above, 4 ml. aliquots of appropriate broth dilutions of phage-containing solution are pipetted into test tubes of 15 mm. inside diameter. For each run there are included 4 ml. amounts of standard phage ( $1 \times 10^{10}$  units/ml.) diluted to  $10^{-3}$ ,  $10^{-4}$ ,  $10^{-5}$ , and  $10^{-6}$ . To all tubes are added 1 ml. portions of a broth suspension of fresh staphylococcal culture containing  $12.5 \times 10^7$  organisms per ml. The tubes are placed in a water bath shaker maintained at  $36^\circ \text{C}$ . and after 1.5 hours turbidity readings are made at 0.2 hour intervals until lysis begins. The tubes are read against formalized broth suspensions of staphylococci ranging from  $5 \times 10^7$  bacteria/ml. to  $20 \times 10^7$  bacteria/ml. Once lysis begins, turbidity comparisons are made at 0.1 hour intervals. The time at which each suspension is reduced to a turbidity end point of  $8 \times 10^7$  cells/ml. is noted. The data obtained from the dilutions of standard phage are plotted as logarithms of initial phage concentrations against the time of lysis (time to reach the arbitrary turbidity end point). This gives a standard curve from which the time of lysis of any unknown solution can be directly converted into original concentration of phage.

Northrop has devised a modification of the activity assay for use with concentrated non-sterile lysates. His unit is the quantity of phage necessary to cause lysis of 5 ml. of standard bacterial suspension ( $0.3 \text{ mm.}^3$  of centrifugally packed cells per ml.) in 1 hour at

$35^\circ \text{C}$ ; it is equivalent to  $10^{10}$  Krueger units.

The activity determination has been used extensively by Kruger and his co-workers, Northrop, Clifton and Morrow, Lin, Fischer and others. With it one can obtain reproducible accurate results in three to four hours instead of twenty-four to forty-eight as in the case with the plaque method. However, it can not be adapted to all organisms inasmuch as it requires fairly rapid growth and complete lysis.

The significance of quantitative data secured by application of phage analytical procedures depends upon the method employed. With the plaque count one cannot distinguish between a single phage molecule and a thousand such molecules grouped together. On the other hand the activity assay determines the total phage present no matter what the state of aggregation.

## GENERAL FEATURES OF THE PHAGE-BACTERIUM REACTION

### 1. The Mechanism of Phage Action on a Susceptible Bacterial Substrate

The following general relationships have been found to obtain in studies on certain strains of *Staphylococci*, colon bacilli, dysentery

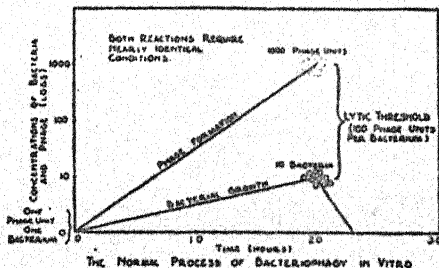


Fig. 1. Phenomena that comprise bacteriophagy.



bacilli and *B. megatherium* conducted by the investigators enumerated in the preceding section.

(a) Bacterial reproduction follows the normal growth curve just as though no phage were present up to the time lysis (massive dissolution) of bacteria begins.

(b) Phage production proceeds at a rate considerably faster than bacterial growth; therefore the ratio of phage to bacteria in a given mixture is constantly rising.

(c) When approximately 100 phage units/bacterium have accumulated, lysis of bacteria occurs very rapidly. This lytic threshold varies with the organisms studied and with the conditions under which the experiments are conducted. Terminal lysis is a spectacular phenomenon resulting in the complete destruction of millions of bacteria in each cubic centimeter of broth within a period of half an hour. It involves actual cellular disruption accompanied by hydrolytic cleavage of bacterial proteins in some instances. Granular cellular debris may or may not remain after lysis has gone to completion depending on the nature of the organism lysed.

(d) The finished lysates may contain as much as 10,000,000 times the initial concentration of phage.

(e) Substances in solution during the reaction may alter the lytic threshold in interesting fashion. For example, small amounts of manganous chloride reduce the phage/bacteria ratio requisite for lysis from 100 to 12; sodium sulfate and sodium chloride have just the opposite effect raising the ratio to as much as 1,000.

(f) By adjusting environmental conditions it is possible to produce

phage in the absence of bacterial growth or to cause organisms to grow in the presence of phage without forming more phage.

(g) Delbrück and Ellis have made a careful study of the reaction between a strain of *B. Coli* and its homologous phage. They observed that the process of phage production is discontinuous and occurs in well-defined steps. The increases (in phage) develop very rapidly and seem to depend upon liberation of phage by cellular lysis.

## 2. Ancillary Phenomena

Phages exhibit decided limitations in the range of their activity; that is, no single phage is capable of lysing all organisms. Usually it is found that a particular phage will act on one group of bacteria but not on others, e.g., a coli phage will not lyse staphylococci. Even within the group for which it displays activity there occur resistant strains able to grow in concentrated phage solution. Apparently phage specificity is linked with the antigenic structure of the bacterial host; certain definite chemical components must be present on the cell surface for phage fixation to occur and if these materials are lacking this highly essential initial step in the phage-bacterium reaction cannot be consummated. Phages have been isolated for species of the following genera: *Actinomyces*, *Corynebacterium*, *Vibrio*, *Micrococcus*, *Bacillus*, *Bacterium*.

Likewise there exist tremendous differences between phages which act on the same host species. These differences extend to particle size, dimensions of plaque produced, antigenic composition and resistance to physical and chemical agents.

When phage-lysed broth cultures are maintained in the incubator for long periods of time secondary growths of bacteria may sometimes develop. These consist of phage-resistant bacteria which usually exhibit a wide variety of altered characters. The dissociated strains may possess entirely different structural, biochemical, pathogenic and immunologic characteristics. Such alterations are reflected in changed colonial structure, fermentative capabilities and host invasiveness. The transfer of a secondary culture to bouillon results in a growth in which resistant bacteria and phage coexist—the so-called “mixed” culture. Secondary cultures do not represent a permanent resistant state, for the capacity to resist phage action may readily be lost if the bacteria are repeatedly transferred to new media or if phage is eliminated from the mixture in some way.

Some strains of bacteria are phage carriers (lysogenic). That is, they live in close association with phage and when the cultures are filtered, phage can be detected in the filtrates. Despite the fact that lysogenic organisms constantly produce phage in the course of their metabolic activities, they display no evidence of damage. Systematic studies have shown that the lysogenic state is not at all uncommon and that the host cannot be divested of its phage-forming function. Every cell of a lysogenic strain produces phage and in spore-formers this tendency is carried through the spore stage.

#### GENERAL PROPERTIES OF PHAGE

Phages are readily inactivated by a wide variety of chemical agents.

In some instances chemical inactivation has been proven to be reversible. For example staphylococcal phage completely inactivated in 2.8%  $\text{HgCl}_2$  may be restored to its original titre by precipitation of the  $\text{Hg}^+$  ion.

When phage solutions are heated the loss of activity proceeds logarithmically with time and in some instances heat inactivation is reversible. The critical thermal increment for anti-staphylococcal phage is 101,000 calories. Exposure of phage to large doses of X-rays (circa 50,000r) results in loss of activity by two mechanisms, an indirect inactivation due to some decomposition product of water and a direct effect ascribable to ionization within the phage molecule. Since the indirect effect can be suppressed by the addition of a protective foreign protein, it is possible to calculate the sensitive volume of the phage molecule with minimal inaccuracy. Values of the sensitive volume determined in this manner agree well with data derived from diffusion, centrifugation and ultrafiltration experiments. Phage inactivation induced by sonic waves follows the equation for a monomolecular reaction. The presence of homologous organisms during treatment of phage with sonic waves tends to inhibit phage destruction.

The specific inhibition of phages by bacterial extracts and cellular autolysates has been the subject of considerable study. Treatment of the inhibiting extracts with acid enhances the inactivating capacity. The polysaccharide nature of the inhibitor has been proven in some instances.

There is no evidence that phages

possess an independent metabolism. Within the range from pH 3.4 to pH 12.0 they carry a negative electrical charge and below pH 3.4 the charge tends to become positive although measurements are made difficult in this zone by the inactivating effect of  $H^+$  ions.

Of particular significance in connection with the therapeutic use of phage (*vide infra*) is the inactivating effect of those products which occur in tissues as a constant part of the phenomenon of inflammation. It is known that blood serum, white cells, whole dead bacteria, tissue debris and in fact colloidal suspensions of many sorts exert either a direct destructive action on phage or an indirect inhibitory effect on the interaction of phage and bacteria.

Phage lysates serve as antigens, i.e., when injected into animals they evoke the formation of antibodies. These antibodies are of two kinds, those which act on phage and those which are specific for the cellular components. The antibacterial antibodies may be absorbed by bacteria but the phage antibodies cannot be so absorbed. Of great theoretical importance is the fact that the antigenic structure of a phage, i.e., its serological character is independent of the substrate on which it is grown.

Experimental evidence has been advanced for the view that bacteria synthesize an inert protein precursor which is converted into active phage protein by an autocatalytic reaction. While such a precursor has not been isolated as yet, its presence can be demonstrated in "activated" bacteria, i.e., cells which have completed a phase of rapid growth and subsequently have been

brought to a resting state by storage in salt solution at low temperature. The addition of these cells to phage results in a very prompt increase in phage titre to levels as high as ten times the original value. The cellular component responsible for this increase is very labile and can be inactivated by several chemicals such as iodoacetic acid and methylene blue + light in concentrations that are not lethal for the cells themselves. The same thing holds for the heat inactivation of precursor; it proceeds at temperatures too low to injure the bacteria and the rate of inactivation rises abruptly with small temperature increments. The critical thermal increment for heat inactivation of phage precursor is 90,000, indicating that the reaction involves protein denaturation.

The purified material obtained by Northrop from lysed staphylococcal cultures has the composition of a nucleoprotein as evidenced by the analytical data in the accompanying table.

C	N	H	P	Acid	Phosphate	Alkaline
40.8	5.4	16.5	4.6	13.0		
41.0	5.2	16.1	5.0		1.5	0.1

An amount of this phage corresponding to  $1 \times 10^{-13}$  milligrams protein nitrogen is sufficient to cause lysis. If this quantity represents 1 molecule it follows that the molecular weight of this particular phage would be three hundred million. The sedimentation constant of staphylococcal phage protein was found to be  $S_{20} = 650 \times 10^{-13}$  which also corresponds to a molecular weight of about three hundred million. The diffusion coefficient of

this phage protein is not constant but varies with the concentration. Apparently the concentrated solutions contain units having a molecular weight of about three hundred million but dilute solutions contain units with a molecular weight of only four hundred thousand. There is strong evidence that phage activity is a specific property of the purified protein.

Pictures of phages taken with the electron microscope show that they consist of a round head and a much thinner tail which gives them a curious sperm-like appearance. There appear to be patterns of granules within the head. The phages adhere to susceptible bacteria either by the head or by the tail.

### THE USE OF PHAGE IN CLINICAL MEDICINE

#### 1. As a Diagnostic Aid

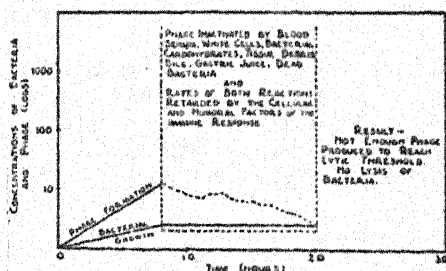
Craigie and Yen have developed a method for typing typhoid bacilli which is based on certain peculiarities of a strain of phage specific for the Vi form of the typhoid bacillus. It has a selective affinity for the particular strain of *E. typhosa* on which it is propagated and for epidemiologically related strains. This phage, known as type II Vi phage does not act on the W form of *E. typhosa* nor on other pathogenic or normal inhabitants of the intestinal tract of man. By using this phage it has been possible to divide freshly isolated cultures into a limited number of readily distinguished types.

The typing of typhoid strains is of real epidemiological importance. All clinical cases arising from a single carrier will show the same type of organism as the carrier and if all carriers in a given area are

typed during an outbreak it is possible to immediately eliminate some of them from consideration and to direct attention to the activities of other carriers. Typing will permit the detection of two or more concurrent outbreaks and in addition will effect the separation of endemic and epidemic cases. In a given epidemic if all cases show the same type of organism, a carrier is probably responsible whereas the detection of a variety of types would imply sewage contamination.

The natural occurrence of anti-dysentery phage in stools at times during the course of bacillary dysentery has been recommended as a diagnostic aid. In one outbreak of institutional dysentery due to the Hiss-Y strain the homologous phage was found in 33% of cases in the first week, 80% in the second, and 45% in the third. Experience in this field has not given uniformly good results and further work is required before the procedure can find widespread application.

#### 2. As a Therapeutic Agent



THE FACTORS WHICH INHIBIT BACTERIOPHAGY IN VIVO  
Fig. 2.—Reasons for failure of lytic destruction of bacteria in tissues.

Recently a survey of the applications of phage to treatment of disease was made by Krueger and Scribner at the request of the Council of Pharmacy and Chemistry of the American Medical Association. They concluded that, with cer-

## DICTIONARY OF BIO-CHEMISTRY

tain special exceptions, the lytic destruction of bacteria by phage in vivo is subject to serious limitations (see Figure 2 above). In their estimation there are four significant mechanisms attending the use of crude lysates; namely non-specific protein shock, local immunization,

specific immunization by means of antigenic substances in the lysate, and promotion of phagocytosis. Figure No. 3 shows the possible mechanisms advanced as the basis for phage action in vivo and evaluates their relative importance.

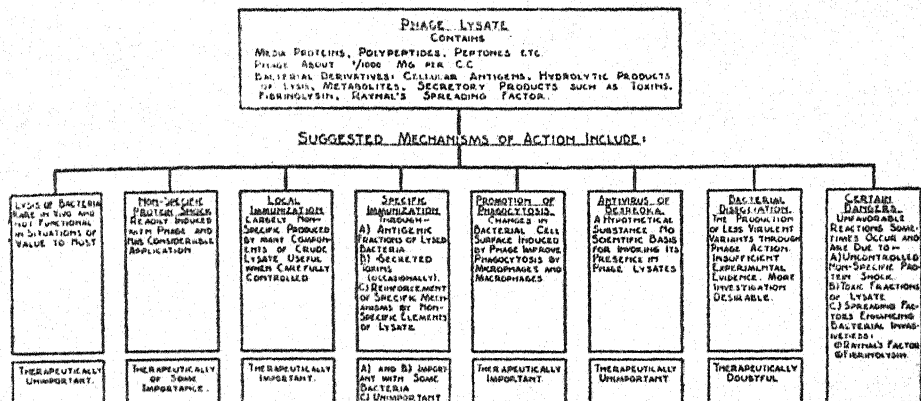


Fig. 3—Possible mechanisms that have been advanced as a basis for phage action in vivo. The evaluation of the importance of each mechanism represents the opinion of the authors.

The reported data on the use of phage in various diseases caused by bacteria are, for the most part, insufficient to establish phage therapy as a method of choice. Only rarely have these studies included an adequate bacteriologic back-ground, control groups or careful comparison with accepted therapeutic procedures. There is evidence, however, that a properly prepared lysate can serve satisfactorily as:

(a) A vaccine for the treatment of certain diseases, e.g., some types of staphylococcal lesions.

(b) An aid for the induction of non-specific protein shock in syndromes in which at times such shock may be used to good purpose, e.g., typhoid fever.

(c) A measure for enhancing the general resistance of an infected

area when applied topically. This depends on the non-specific action of the lysate in mobilizing macrophages and microphages.

Phage solutions possess no measurable degree of superiority over well-known and accepted preparations employed for the same purposes; for example, bacterial vaccines and toxoids in carbuncles and furunculosis or typhoid vaccine in non-specific shock therapy. Modern chemotherapeutic approaches to the treatment of a variety of conditions for which phage has been recommended (bacteremias, gonorrhea, cystitis) offer more chances of success than does phage.

The literature cites numerous accounts of reactions ranging from mild to severe following the injec-

tion, local application or ingestion of phage and animal experimental work has shown that lysates may contain enough soluble toxin or Reynal's spreading factor to be actually dangerous. Thus the use of phage in any individual case should be undertaken with caution and with the above mentioned limitations in mind.

In bacillary dysentery and cholera there is some evidence that phage may be of value. Here again much additional work is required before phage can be established as a therapeutic agent of choice.

\*The opinions advanced in this paper are those of the author and do not represent the official views of the Navy Department.

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#### SELECTED REFERENCES

<sup>1</sup> Bronfenbrenner, J. J. Bacteriophagy in T. M. River's "Filterable Viruses." Williams and Wilkins Co., Baltimore. 1928.

<sup>2</sup> Burnet, F. M. Bacteriophage and Cognate Phenomena. Vol. VII, A System of Bacteriology. Med. Res. Council. Published by H. M. S. Office, London. 1930.

<sup>3</sup> Delbrück, M. Chapter on Bacterial Viruses (Bacteriophages) in "Advances in Enzymology." Vol. II. Interscience Publishers Inc. 1942.

<sup>4</sup> d'Herelle, F. "The Bacteriophage and Its Behavior." Trans. by G. H. Smith. Williams and Wilkins Co., Baltimore.

<sup>5</sup> Krueger, A. P. The Nature of Bacteriophage and Its Mode of Action. Physiological Reviews. 1936. 16: 129.

<sup>6</sup> Krueger, A. P. and Scribner, E. J. The Bacteriophage: Its Nature and Its Therapeutic Use. J.A.M.A. May 10,

1941, 116: 2160; May 17, 1941, 116: 2269.

<sup>7</sup> Northrop, J. H. Chapter VII, Bacteriophage, in "Crystalline Enzymes, the Chemistry of Pepsin, Trypsin and Bacteriophage." Columbia University Press.

#### BACTERIOTROPIN

Substance in blood serum which makes bacteria more susceptible to engulfment by phagocytes; opsonin.

#### BAEYER-DREWSSEN TEST FOR ACETONE

Acetone produces a blue color when a solution of it is treated with o-nitrobenzaldehyde and heated to boiling, followed by the addition of a few drops of sodium or potassium hydroxide solution. Reference: Ber. 15, 2856 (1882). Arch. klin. Med. 34, 132 (1883). Chem. Ztg. 1889, 84. J. Soc. Chem. Ind. 51, 276T (1932).

#### BAEYER'S TEST

A test for dextrose.

#### BAICALIN

C<sub>21</sub>H<sub>16</sub>O<sub>11</sub>, a glycoside of glucuronic acid and 5, 6, 7-trihydroxyflavone, present in the roots of *Scutellaria baicalensis*.

#### BAKHAR

An enzyme used in the manufacture of rice beers.

#### BALATA

Rubber-like material from the latex of S. American *Mimusops balata*.

#### BALDNESS

See Hair.

#### BALJET REACTION FOR DIGITALIS GLUCOSIDES AND STROPHANTHINS

Digitoxin, gitalin and g- or k-strophanthin yield a red to orange color, at room temperature, with the following reagent — a freshly



prepared mixture of a 1% alcoholic solution of picric acid with an equal volume of carbonate-free 10% sodium hydroxide solution.

Reference: Schweiz. Apoth.-Ztg. 1918, 71. Zeit. allgem. osterr. Apoth.-Ver. 1920, 189.

# **BALSAM OF PERU**

Extract of Myroxylon Pereirae containing benzyl benzoate and cinnamate, used as antiseptic.

# **BALSAM OF TOLU**

A semi-solid extract of Myroxylon toluifera, used as an antiseptic expectorant.

# **BAMBOO**

A woody grass.

# **BAPTISIN**

Glycoside of the roots of Baptisia tinctoria, which upon hydrolysis yields rhamnose and a complex flavone.  $C_{26}H_{32}O_{14}$ .

# **BARAC REACTION FOR ASCORBIC ACID**

Ascorbic acid, in alkaline solution, produces an orange color with diazotized sulfanilic acid. The acid functions as a reducing agent, evolving nitrogen from the reagent.

Reference: Compt. rend. soc. biol. 126, 61 (1937).

# **BARBALOIN**

The active principle of aloes, a glycoside of d-arabinose and al-phahydroxy-anthraquinone.

# **BARBITAL**

Veronal; barbitone; an odorless, slightly bitter, white powder,  $C_8H_{12}O_3N_2$ , diethylmalonyl urea or diethylbarbituric acid, m. p. 188-190°, used as a hypnotic.

# **BARBITURATE POISONING**

See Toxicology.

# **BARBITURATE TEST**

See Dille-Kopanyi.

# **BARBITURIC ACID**

Malonyl urea; a soporific and parent substance of many soporifics, m. p. 253°.

# **BARDACH TEST FOR BLOOD IN URINE**

5 cc. of urine are treated with 3 drops of 30% acetic acid, allowed to stand 2 minutes and 2 drops of saturated alcoholic solution of guaiac resin added. After shaking, 0.5 gm. sodium perborate are added, 3 cc. 80% acetic acid quickly added, the solution shaken and overlaid with 2-3 cc. alcohol and 1-2 drops pyridine. Blue color, forming near pyridine, indicates blood.

Reference: Chem.-Ztg. 1913, 1190.

# **BARFOED REAGENT AND TEST FOR GLUCOSE**

Glucose forms a red precipitate of cuprous oxide when a solution of it is boiled with a few drops of reagent for a short time. Reagent — 13.3 gm. of neutral crystalline cupric acetate are dissolved in 200cc. of 1% acetic acid.

0.1% glucose in dextrin may be detected.

Reference: Zeit. anal. Chem. 12, 27 (1873). J. prakt. Chem. (2) 6, 334. J.A.C.S. 29, 1744 (1907); 37, 2227 (1915).

# **BARGER-BERGER-TODD THIOCHROME REACTION FOR VITAMIN B<sub>1</sub>**

A dilute solution of vitamin B<sub>1</sub>, treated with a very dilute solution of potassium ferricyanide followed by sodium hydroxide, gives rise to blue fluorescence, due to the formation of thiochrome.

Reference: Nature, 136, 259 (1935); 135, 107 (1935). Rec. trav. chim. 55, 1046 (1936).

**BARM**

A fermented wort used as a leaven.

**BARNACLES**

Crustaceans which attach themselves to surfaces in adult stage.

**BARRAL TEST FOR ALBUMIN AND BILE PIGMENTS IN URINE**

Filtered urine is floated on a 20% solution of o-phenolsulfonic acid. Formation of a green ring indicates bile pigments, albumin forms a white ring. Sensitivity 5 mg. albumin per liter.

Reference: Pharm. Zentralhalle 1898, 28.

**BARRAL'S TEST**

A test for albumin and bile pigments.

**BARRET TEST FOR ACETONE IN URINE**

Immediate formation of a precipitate when urine or blood filtrates are slowly distilled into dilute (7:1) Nessler's solution indicates the presence of acetone.

Reference: Biochem. J. 30, 888 (1936).

**BARTLEY TEST FOR BILE IN URINE**

Bile pigments in urine impart a green color to the clear filtered solution when treated with hydrochloric acid and ferric chloride. Shaking with chloroform removes any blue color due to indican.

Reference: Pharm. Rundschau 1901, 239. Pharm. Zentralhalle 1911, 899, 1028. Rev. intern. med. chir. 1913, 133. J.A.M.A. 1924, 687.

**BASAL GANGLIA**

Masses of gray matter at base of cerebral hemispheres.

**BASAL METABOLISM**

The minimum respiratory metabolism which can be expressed most

satisfactorily in terms of calories per square meter of body surface per hour. The measurement is made on completely relaxed subject lying down following preliminary rest period, 15 to 18 hours after eating in a warm room. The subject should not be asleep.

See Standard Metabolism

**BASEDOW'S DISEASE**

See Goiter.

**BASES, PHYSIOLOGICAL, TEST FOR**

See Zimmermann.

**BASHAM'S TEST**

A test for bile pigment.

**BASIDIOMYCETES**

See Cellulose Decomposition, Microbiology.

**BASOPHIL (BASOPHILE)**

Cells which stain with basic dyes.

**BATHYSMAL**

Pertaining to deepest sea depths.

**BATRACHIANS**

Amphibians.

**BATYL ALCOHOL**

An active principle of bone marrow, found in fish oils; octadecyl monoether of glycerine.

**BAUER LIVER FUNCTION TEST**

In abnormal liver function galactose, orally administered, is excreted in the urine.

Reference: Wiener med. Wochenschr. 1906, No. 1.

**BAYER REACTION FOR ADRENALINE**

A solution of 2 cc. adrenaline, 1 cc. sulfanilic acid solution, 2 cc. sodium biiodate solution and 1 cc. 10% phosphoric acid solution is colored reddish-yellow if adrenaline concentration is 1:50000; yell-

ow at dilution of 1:625000; yellowish at 1:830000. Yellow color is visible up to 1:5000000 dilution.

Reference: Biochem. Zeit. 20, 183.

#### BAYER 205

Germanin; Fournneau 309; a modified trypan blue dye with peptide linkages, used in treating trypanosome diseases.

#### BAYER-205 TEST

See Steppihn-Utkin-Ljubowzow.

#### BECHER TEST FOR KIDNEY INSUFFICIENCY

2 cc. of filtered blood serum, made protein-free by precipitation with trichloroacetic acid, is boiled with 0.5 cc. concentrated nitric acid for 0.5 minute, cooled, treated with 1.5 cc. 33% sodium hydroxide solution and diluted to 4 cc. with sodium hydroxide. Positive test is indicated by yellow color which may be compared colorimetrically with 0.03874% potassium dichromate solution.

Reference: Deut. Arch. klin. Med. 148, 10 (1925). Münch. med. Wochenschr. 74, 134 (1927).

#### BECQUEREL RAYS

Radioactive rays.

#### BEHENIC ACID

N-docosanoic acid; a saturated fatty acid,  $\text{CH}_3(\text{CH}_2)_{20}\text{COOH}$ , found in oil of ben from seeds of *Moringa pterygosperma*, m.p.  $84^\circ$ .

#### BEILSTEIN TEST FOR HALOGENS IN ORGANIC COMPOUNDS

A halide-free copper spiral is dipped into the organic substance, ignited, and the substance allowed to burn outside the flame. A green color, when the spiral is heated in the non-luminous portion of the flame, is a positive test.

Reference: Ber. 1872, 620. Ind. Eng. Chem. Anal. Ed. 11, 250 (1939).

#### BELL TEST FOR ALUM IN FLOUR OR BREAD

5 gm. of flour are mixed with 5 cc. water and 1 cc. saturated ammonium carbonate solution and 1 cc. of reagent are added. Lavender to blue color, depending upon amount of alum, is developed. Pure flour yields light red color, rapidly becoming dirty brown. Reagent—Freshly prepared logwood tincture from 5 gm. logwood and 100 cc. alcohol.

Reference: Arch. Pharm. 1885, 254. Giorn. farm. Chim. 1910, 49.

#### BELLADONNA

Deadly nightshade extract containing the active principle hyoscyamine, an antispasmodic.

#### BENCE-JONES PROTEIN

A protein of bone marrow and leukocytes and found in the urine in leukemia, eczema and multiple myelomata, coagulates under  $55^\circ\text{C}$ . and redissolves on boiling; molecular weight about 35,000.

See also Myelopathic Albumose.

#### BENDS, THE

See Caisson Disease.

#### BENEDICT-DENIS METHOD

A method for the determination of total sulfur, frequently applied to urine.

#### BENEDICT-HOPKINS-COLE REAGENT

250 cc. of saturated solution of oxalic acid are added slowly, while cooling, to 10 gm. of magnesium powder. The solution is filtered, made acid with acetic acid and diluted to 1 liter.

Reference: J. Biol. Chem. 6, 51 (1909). J. Physiol. 27, 418 (1901).

#### BENEDICT REAGENTS FOR REDUCING SUGARS

The reagent consists of two solutions. I. (a) 69.3 gm. copper sul-

fate dissolved in 1000 cc. of water. (b) 346 gm. Rochelle salt and 200 gm. anhydrous sodium carbonate in 1000 cc. of water. (c) 200 gm. potassium thiocyanate in 1000 cc. of water.

Equal volumes of the solutions are mixed in the order indicated for use. 2.5 to 5 gm. of anhydrous sodium carbonate are added to each 30 cc. of the resulting solution. II. 173 gm. of sodium citrate. and 100 gm. of anhydrous sodium carbonate are dissolved, by heat, in 600 cc. of water, the solution filtered and diluted to 850 cc. 17.3 gm. of copper sulfate are dissolved in 150 cc. of water and added slowly, with stirring, to the carbonate-citrate solution in a large beaker. The solution is ready for use.

To test for glucose, 8 drops of urine are treated with about 5 cc. of reagent, the solution boiled for 1-2 minutes and cooled. A voluminous red, yellow or green precipitate indicates glucose.

Reference: J. Biol. Chem. 5, 485, (1908). Boll. chim.-farm. 1923. Pharm. Ztg. 1923, 706.

See also Glycosurias, Non-Diabetic.

## BENTHOS

Flora and fauna of sea bottom.

## 1,2-BENZANTHRACENE

See Carcinogenetic Hydrocarbons.

## BENZANTHRACENE DERIVATIVES, ESTROGENIC ACTIVITY OF

See Estrogens, Synthetic.

## BENZEDRINE

$\beta$ -phenyl isopropylamine; a compound related to ephedrine and epinephrine; orally acts as a stimulant, increasing rapidity and intensity of heart action; on inhalation causes shrinkage of mucous membrane.

## BENZOPHENONE DERIVATIVES OF

See Estrogens, Synthetic.

## BENZOYL PEROXIDE, TEST FOR

See Lejeune.

## 1, 2,-BENZPYRENE

A carcinogenic hydrocarbon found in coal tar; shows characteristic fluorescence spectrum bands at 4180, and 4400 Å.

## BERBERINE

An alkaloid from various plants, relatively inactive,  $C_{20}H_{19}O_5N$ .

## BERIBERI

Avitaminosis  $B_1$ ; hypovitaminosis  $B_1$ , a disease due to lack of vitamin  $B_1$  in the diet or to failure to absorb it. The symptoms are loss of strength, neuritis, edema, myocardial degeneration and muscular atrophy. There is a dry or paralytic type (atrophic) and a dropsical (wet) type, also cardiac forms and "infantile beriberi," which is acute. The treatment is dietary or by direct administration of the vitamin.

## BERTHELOT REACTIONS

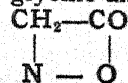
See Digitalis.

## BERTRAND'S REAGENT FOR ALKALOIDS

Alkaloids form insoluble precipitates with silicotungstic acid, the sensitivity varying with different alkaloids from 1:8000 to 1:500000. Reference: Compt. rend. 128, 742 (1899).

## BETAINE

The simplest member of the group of betaines; it is derived from glycine and has the formula



$(\text{CH}_3)_3$   
found in beet sugar, etc.

**BETAINE TEST**

See Neuberg.

**BETAINES**

A group of completely methylated heterocyclic  $\alpha$ ,  $\beta$ , and  $\gamma$ -amino acids found distributed in the plant kingdom.

See Betaine.

**BETA PARTICLE**

High velocity electrons ejected in nuclear decomposition.

**BETITOL**

Tetritol obtained from beet molasses;  $C_6H_8(OH)_4$ ;  
M. P. 224°.

**BEZSSONOV REACTION FOR ANTISCORBUTIC EXTRACTS AND POLYPHENOLS**

Reagent — 2.7 gm. phosphomolybdic acid and 44 gm. sodium tungstate heated with 5 cc. 85% phosphoric acid, 60 cc. 5 normal sulfuric acid and 400 cc. water for 2 hours at 50-60°.

A blue color is obtained with all vegetable antiscorbutic extracts. Of the monophenols, only guaiacol reacts, forming a yellow-brown color. Hydroquinone gives an intense blue; catechol red-violet turning blue; orcinol and resorcinol no color; protocatechuic acid, pyrogallol and tannin yellow-brown; phloroglucinol gives no reaction.

Reference: Compt. rend. 173, 466 (1921). Bull. soc. chim. biol. 4, 83 (1922).

**B.I.**

Buffer index; the ratio of a small increment of alkali and the small increment in pH brought about by its addition. If acids are used negative values can be used in both cases, thus always giving a positive index.

**BIAL REAGENT AND TEST FOR PENTOSE IN URINE**

Not more than 1 cc. of urine is added to 5 cc. of reagent, after the latter has been boiled; a green pigment, extractable with amyl alcohol, indicates pentoses. Reagent — 1-1.5 gm. orcin are added to 300 gm. 30% hydrochloric acid, to which has been added 25-30 drops of 10% ferric chloride solution.

Reference: Deut. med. Wochschr. 1902, 523. Biochem. Zeit. 3, 323.

**BIAL'S TEST**

See Glycosurias, Non-Diabetic.

**BICEPS**

Muscle with two heads.

**BIENNIAL**

A plant fruiting every two years, storing food in the interim.

**BILE**

A bitter yellow fluid, secreted by liver cells of practically all vertebrates and stored in most species in the gall bladder, where it is considerably concentrated by absorption of water, with a change of its reaction from slightly alkaline to weakly acidic, it is eventually excreted into the duodenum, whence its essential constituents, the bile acids, return to the liver. The most important components of this aqueous solution, besides the alkali salts of the bile acids, are alkali carbonate, bile pigments, lipids, including cholesterol, and mucin. Bile is an emulsifying agent for lipids, thus essential for their digestion (See H. Sobotka, Physiological Chemistry of the Bile, Baltimore 1937.)

HARRY SOBOTKA.

See Gastro-Enterology.

**BILE ACIDS**

Those constituents of bile that keep water insoluble fats in solution or dispersion; they exist

in the bile as the sodium salts of the acids conjugated through a peptide linkage with glycine and taurine; they are all derived from the same nucleus, cholic acid, but have hydroxyl groups at different positions.

See Steroids.

See Drechsel, Pettenkofer.

## BILE PIGMENTS

A series of tetrapyrrole pigments, found in the bile, and resulting from the destruction of hemoglobin by oxidative splitting of the porphyrin ring system at one methine ( $-\text{CH}=\text{}$ ) group and removal of the iron and globin component. See bilirubin, biliverdin, bilicynanin.

## BILE PIGMENTS, TESTS FOR

See Barral, Bartley, Chabrol-Charonnet, Cole, Ehrlich, Fouchet, Giemsa, Kuhn, Marechal, Rosenberg, Salkowski, Travaille.

## BILE SALTS

The alkali salts of the bile acids; they form soluble addition products with fatty acids which are diffusible; in addition, they lower surface tension, allowing for more facile diffusion and attack of lipids by lipases.

## BILE TRACT DISEASE

Cholecystitis; cholangitis; cholelithiasis; dyskinesia of the bile passages; a group of disorders of the bile passages which may be characterized by the inflammation of the gall bladder (cholecystitis) or of the bile passages (cholangitis) or the formation of "stones" or calculi in the gall bladder or bile ducts (cholelithiasis) in both acute and chronic forms. The origin of these diseases may be due to infection by various bacilli, e.g. streptococcus, typhoid, bile stasis, dietary upsets

leading to separation of cholesterol, especially in "gallstones" (cholelithiasis). An entire science of cholecystography has been developed to visualize the stones by means of dyes opaque to X-rays, which usually contain high percentages of iodine. Jaundice is frequently an accompaniment of biliary disease because of liver involvement. The symptoms include "biliousness" which is characterized by nausea, headaches, drowsiness, belching. Gall stones are largely cholesterol with protein inclusions. In treatment the flow of bile can be increased only cautiously. The agents used to promote the flow of bile, cholagogues or cholekinetics, are usually magnesium salts. Substances which tend to increase the amount of bile secreted, or choleretics, may be salicylates or cinchophen combined with the bicarbonates and sulfates.

Numerous tests have been developed in connection with bile tract and liver diseases besides cholecystography. Bile pigments are determined in the blood and in the urine, e.g. the van den Bergh test (which see). For urobilinogen one uses the Ehrlich aldehyde reagent (which see). Various types of jaundice (hemolytic, obstructive, parenchymatous) are thus distinguished. Liver function is also tested by ability of the liver to store glycogen from galactose, blood sedimentation tests, amino acid tests to determine breakdown of tissue, and special tests on serum proteins, e.g. Takata-ara reaction.

## BILE, WHITE

White bile is found as the contents of the gall bladder when the



flow of bile from the liver into the extrahepatic bile duct system is obstructed. It contains inorganic salts and mucus excreted by the wall of gall bladder and ducts.

HARRY SOBOTKA.

# BILICYANIN

A blue bile pigment found in pathological conditions such as gall-stones; it is a porphyrin derivative with the 4 pyrrole nuclei in a straight-line arrangement, resulting from the oxidation of biliverdin.

# BILIFULVIN,

# BILIPHAEIN

See Bilirubin.

# BILIFUSCIN

A brown bile pigment,  $C_{16}H_{20}O_4N_2$ , m.p.  $183^{\circ}$ .

# BILINEURINE

See Choline.

# BILIRUBIN (BILIFULVINE,

# BILIPHAEIN)

$C_{33}H_{36}N_4O_6$ ; a porphyrin derivative with the 4 pyrrole nuclei in a straight line arrangement; it is formed by the destruction of hemoglobin; on oxidation the red bilirubin yields green biliverdin.

# BILIRUBIN TESTS

See Franke, v. Purjesz, Van den Bergh.

# BILIVERDIN

$C_{33}H_{36}N_4O_6$ ; a green bile pigment found in the uterus and in feces; it is a porphyrin derivative with the 4 pyrrole nuclei in a straight line arrangement, resulting from the oxidation of bilirubin; on oxidation biliverdin yields blue bilicyanin.

# BIOCHEMICAL GENETICS

See Genetics, Biochemical.

# BIOCHEMISTRY

Definitions and Classifications of Branches. Biochemistry is a hybrid science. It arose from the overlapping of more or less purely chemical issues and more or less biological issues. Consequently it is subject to a great variety of definitions reflecting the scope of the pure sciences and the manner in which they are combined. The manner of combination results either in an emphasis on biology or on chemistry. "Biochemistry" is a term which stresses chemistry and to most biochemists, at least of two or three decades ago, it meant "the chemistry of biologically important substances." The emphasis has been shifting to "the chemical aspects of living processes" and, we venture to predict, will lead to the employment of the expression "chemical biology." This is a trend in all scientific development and has led, for example, in the borderland between physics and chemistry, to the emergence of two subjects, "physical chemistry" and "chemical physics." Thus, we can expect another pair, "biological chemistry" (or biochemistry) and "chemical biology," to divide the field now customarily described by the former term. The term "physiological chemistry," designed possibly to call attention to the dynamics of the biological processes has been falling into disuse, because physiology is after all only one branch of biology. If it is retained it may become a branch of "biological chemistry."

It is possible also that "chemical biology" might receive a name like "chemobiology." The trend toward renaming in the direction in which "chemical" serves as the adjective is illustrated by the relatively recent

rise of "chemical embryology" (Needham). If we are right, this in itself may become a branch of "chemical evolution" which in turn would be a branch of "chemical biology."

Other definitions of biochemistry emphasize, consciously or unconsciously, the philosophy of the definer. The author of the definition, may be an outright materialist, in which case he would stress the physical basis of life, or an idealist of one kind or another who believes in entelechies, life principles and the like. B. Moore (1921) illustrates the latter in his definition of biochemistry as "the study of the chemical substances produced by biotic energy." One hates to think of what would become of the subject according to such a definition if there were no special distinctive "biotic energy."

The modern trend is toward what the author has called "dynamic biochemistry" before favoring wholeheartedly "chemical biology." What is left behind may well go under the name of "descriptive biochemistry" which is a large part of the Dictionary, which catalogues and describes many of the substances found in living sources.

A convenient, but theoretically poorly founded, distinction is that of a "pure" and an "applied" science. The varieties of "applied biochemistry" include what the medical student gets as "pathological chemistry" or what the botanist might take up as "phytochemistry," the zoologist as "zoochemistry."

There are even more complicated hybrids in such subjects as Vernadsky's "biogeochemistry" and the

loosely defined field of "comparative biochemistry" which ranges over all living types in an evolutionary manner. (Baldwin)

We suggest that order in this creation of sectors of research might be set up by listing the divisions of biology as (1) morphology (2) distribution (3) physiology and (4) aetiology and the customary divisions of chemistry as physical, inorganic, organic, analytical, etc., with subdivisions such as "colloidal" and the like, and then blending them into hybrid sciences. This will account for the appearance of such terms—used in England—as "aetiological chemistry" meaning the division of biochemistry dealing with "cause and effect in the determination of development" and thus naturally including as a part of itself "chemical embryology." In this connection we would prefer "chemical aetiology" or "chemical evolution." New subjects might be, for example, "colloidal chemical physiology" or "chemical genetics" or "chemical immunity." At present these subjects are suggested by expressions like "the biochemistry of genetics," "the biochemistry of the earth," (i.e. of living forms in the earth's development), etc., etc.

W. M. M.

## BIOCHEMISTRY, CLINICAL APPLICATIONS OF

See Clinical Applications of Biochemistry.

## BIOCHEMISTRY, COMPARATIVE

Studies in biochemistry which involve considerations of differences and similarities between species.

## BIOCHEMISTRY, DIVISIONS OF

No rigid, conventional divisions of biochemistry exist, as in the

case of chemistry and physics proper, where a distinction between "organic" and "inorganic," for example, is rather sharp. Still dominant is the treatment where the class of substance involved is the name of the subject, as "Carbohydrates," "Fats," "Proteins," "Inorganic Constituents," "Accessory Substances," and now "Hormones." Almost all texts describe these groups of substances and then take up what is known of their ingestion or synthesis in the body, their role, their metabolism and the further course, final consumption and elimination of the products of their metabolism. That at least the principal classes of materials serve as equivalents of one another and are mutually convertible tends to upset any such classification. The latter part of many a text, therefore, resorts to a series of chapters where the physiological process, e.g. digestion, or the function of an important organ, e.g., the kidney or the liver, serves as the division of the subject. Occasionally a text starts with a physico-chemical introduction in place of the organic chemistry of the principal materials. In such cases a stress on colloid chemistry is imperative. A time is coming when introductions will have to stress a certain amount of new theoretical material from the field of physics, e.g. spectroscopic theory, electron diffraction and its applications in the electron microscope. From this point of view the fields of biochemistry shape up as applications of sectors of the other sciences to living systems.

W. M. M.

## BIOELECTRIC POTENTIALS

See Potentials, Bioelectric.

## BIOGEOCHEMISTRY

A term used by Vernadski for studies involving the factors suggested by the name.

## BIOGEOGRAPHY

The science of the geographical distribution of living things.

## BIOLUMINESCENCE

Bioluminescence is a word applied to the light emitted by various living organisms. At least 40 different orders of animals contain luminous species and two groups of plants, the bacteria, responsible for the luminescence of flesh and dead fish, and the fungi, which live in phosphorescent wood. Luminous bacteria are so small that individuals cannot be seen by their own light but colonies are visible. They are easily cultured and are non-pathogenic to man but may infect living animals, giving rise to a luminescent disease of sand-fleas, shrimps and midges, which is eventually fatal. Luminous bacteria may also live symbiotically in special organs of certain fish, notably Photoblepharon and Anomalops, of the Banda islands.

Bacteria and fungi emit light continuously day and night, while all other forms luminescence only when stimulated. The phosphorescence of the sea appears when many different kinds of small organisms are disturbed by the breaking of waves or motion of a boat. Among the groups of animals containing luminous species are flagellates, radiolaria, sponges, jelly-fish hydroids, sea pens, ctenophores, nemerteans, earthworms and many marine worms, shrimp, ostracods and copepods, myriapods, several groups of insects, molluscs, squid, brittle stars, balanoglossids, tunicates and fish.

Bioluminescence is never dependent on a previous illumination of the cells or a previous radiation of any kind, nor is it connected with crystallization, friction, or rubbing, but is the result of oxidation by molecular oxygen of a definite substance produced in the luminous cell. It is a chemiluminescence. The luminous material or photogen is almost universally manufactured by living cells as granules, which may normally undergo oxidation within the cell, as in the fire-fly, (intracellular luminescence) or be extruded as a luminous slime or secretion (extracellular luminescence) as in a small ostracod crustacean, Cypridina. Most is known concerning the chemistry of extracellular luminescence, especially that of Cypridina.

In Cypridina the granules in the secretion dissolve on contact with sea water and the homogeneous luminescence is emitted by the resultant colloidal solution. Two kinds of granules are distinguishable in the cells of Cypridina, one large and yellow, the other small and colorless. In fact, in five of twenty-five different groups of luminous animals tested, it can be demonstrated that luminescence is due to two chemical substances, luciferin (yellow) and luciferase (colorless), which can be easily separated because of a difference in resistance to heating and other properties.

Crude luciferin solution is prepared by making a hot water extract of a luminous organ. Heating destroys the luciferase but does not harm the luciferin. Crude luciferase solution is prepared by making a cold water extract of a luminous organ, when both luciferin and luciferase dissolve and luminescence

occurs. The extract is then allowed to stand in the air until the light disappears, evidence that the luciferin has been completely oxidized, leaving the luciferase, an enzyme, in solution. A luciferase solution, by virtue of this mode of preparation, must contain the oxidation product of luciferin as well as luciferase.

Luciferin and luciferase are quite specific. Luciferin from one animal will not luminesce if mixed with the luciferase of another luminous form unless the animals are closely related, such as two species of the same genera or two genera within the same order. Even if the color of the luminescence is different in the two different species light will appear, provided the species are closely related. In this case it is interesting to note that the color of luminescence of the resultant "cross" is determined by the animal supplying the luciferase. Luciferase must be the source of the light. It is convenient to designate the luciferins and luciferases by prefixing the name of the animal from which the substances are obtained.

Most luminous animals, if dried rapidly will again luminesce on moistening. Dried Cypridinae have been kept for 26 years without deterioration and can be used for preparing luciferin and luciferase.

Cypridina luciferin is purified by extraction of the dry Cypridinae with methyl alcohol. Ten per cent of butyl alcohol is then added and the methyl alcohol removed in vacuo. The supernatant butyl alcohol extract is chilled and benzoylated with benzoyl chloride. After fifteen minutes this solution is diluted with ten volumes of water and the new inactive benzoyl

luciferin derivatives extracted with pure ether. After removing the ether in vacuo the residual liquor is hydrolyzed with hydrochloric acid in absence of oxygen. The free active luciferin is left in the acid solution and can be extracted with butyl alcohol. By repeating the benzoylation and hydrolysis, a product purified 2,000-fold, as compared with dry *Cypridinae*, can be obtained.

To purify luciferase it is usually sufficient to dialyze a cold, well-stirred water extract of rapidly dried, powdered *Cypridinae* against cold running water for twenty hours. Dialysis removes pigment, and a precipitate forms which can be filtered off. A few drops of toluene added to this solution will preserve it for months with little loss in activity if kept in a refrigerator.

*Cypridina* luciferin is slowly dialyzable; not destroyed by trypsin; soluble in water, absolute methyl, ethyl, and propyl alcohol but insoluble in acetone, benzene and ether; readily adsorbed on fine particles. It does not act as an antigen.

*Cypridina* luciferase is non-dialyzable; destroyed by trypsin; soluble in water, but insoluble in alcohols and all fat solvents; readily adsorbed on surfaces. It is capable of forming an antiluciferase when injected into the blood of a rabbit. Other luciferins and luciferases have different properties.

The oxidation of luciferin with production of light in the presence of luciferase gives an oxidation product which cannot be reduced, whereas the oxidation without luminescence by oxidants like potassium ferricyanide is reversible.

This product is called oxidized luciferin. The change with ferricyanide occurs in two steps, one of which is the reversible oxidation previously referred to; the second is irreversible and probably also an oxidation, although this has not been definitely demonstrated. The spontaneous oxidation of luciferin without emission of light in crude solutions (without luciferase) is probably catalyzed by traces of heavy metals in the solution and proceeds much more slowly when the luciferin has been purified. Both the non-luminescent oxidation and the luminescent oxidation undoubtedly take place simultaneously when luciferin is mixed with luciferase.

Cyanide does not affect luciferase but forms an irreversible combination with purified *Cypridina* luciferin. Azide combines reversibly with luciferin whereas urethane, sulfanilamide, sulphathiazol, sulphapyridine and p-aminobenzoic acid probably act reversibly to inhibit luciferase activity.

Measurements of the absorption spectrum show (a) that freshly dissolved luciferin has an absorption maximum at 430 m $\mu$ , or slightly lower, and is yellow in color; (b) that during oxidation this absorption maximum is rapidly replaced by one at 470 m $\mu$ , which subsequently decreases to give a colorless solution; (c) that in the presence of luciferase these same color changes also occur, but at least one hundred times faster; (d) that the amount of luciferin in a solution (as measured by total luminescence) is directly proportional to the labile color of the solution and not to the total color, and (e) that the ultraviolet absorption decreases in the region 250 to 300 m $\mu$  during



the first stages of nonluminescent oxidation and subsequently increases in the region 320 to 420 mμ.

The ultraviolet absorption spectrum of freshly dissolved luciferin shows inflexions suggesting maxima at 310 to 320 mμ., 280 mμ., and 260 mμ., with practically complete absorption at 240 mμ., and below. If all the absorption is due to luciferin, a benzene or naphthalene structure may be indicated.

The emission spectrum of *Cypridina* luminescence is a continuous band extending from the violet to the yellow with a maximum about 480 mμ.

The kinetics of the decay of luminescence when *Cypridina* luciferin and luciferase are mixed have been extensively studied. If purified solutions are used the decay is logarithmic and light intensity may be used as a measure of reaction velocity (of oxidation of luciferin,  $dx/dt$ ). Under proper conditions the velocity constant is proportional to luciferase concentration and can be used as a quantitative measure of luciferase. The total light emitted is a measure of initial luciferin concentration and can be used to determine luciferin in purification studies.

Kinetics of the rate of appearance of light can be studied by a photoelectric flow method. It is found that the time to reach half the maximum intensity is 0.006 second and full intensity 0.03 second. The half time of decay in these ultra-short flashes may be only 0.12 second, and the decay curve is logarithmic in form.

The above statement applies to conditions where oxygen is already present. If luciferin and luciferase

are previously mixed in absence of oxygen and then this anaerobic solution mixed with aerated water, the time required to attain half the maximum intensity is 0.002 second, and full intensity 0.008 second, three times as fast. The experiment clearly shows that luciferin and luciferase combine slowly, whereas the combination with oxygen is rapid.

Apparently four reactions in series are actually involved when luciferin, luciferase and oxygen react. The steps may be represented as follows:

- (1)  $\text{LH}_2$  (luciferin) + A (luciferase)  $\rightarrow$   $\text{A} \cdot \text{LH}_2$
- (2)  $\text{A} \cdot \text{LH}_2 + \frac{1}{2} \text{O}_2 \rightarrow \text{A} \cdot \text{LH}_2 \cdot \text{O}$
- (3)  $\text{A} \cdot \text{LH}_2 \cdot \text{O} \rightarrow \text{A}'$  (excited luciferase) + L (oxidized luciferin) +  $\text{H}_2\text{O}$
- (4)  $\text{A}' \rightarrow \text{A} + h\nu$  (a quantum of light)

Mathematical analysis indicates that two consecutive monomolecular reactions with the velocity constants,  $k_1$  and  $k_2$  will explain the course of the intensity of the experimental flash with time.

It is thus seen that, on this hypothesis, the oxidation of luciferin is a dehydrogenation and that the luciferase molecules (A) pick up the energy of reaction, becoming excited (A') and emitting their excess energy as a quantum of light on return to the normal state.

Biochemical investigations of luminous bacteria are more difficult to interpret because luciferin and luciferase cannot actually be isolated or demonstrated in these forms and every procedure that breaks up the cells also destroys the luminescence. Light production is believed to be bound up with the cell respiration and luciferin



(assumed to be present) to be a part of the hydrogen transport system. Luminous bacteria require only traces of oxygen for luminescence and can be used as detectors of oxygen. If allowed to stand in absence of oxygen, luciferin accumulates in the cells, since, when oxygen is readmitted, an excess flash of luminescence appears that lasts a few seconds before the normal intensity is attained. If allowed to stand too long in absence of oxygen, the luciferase, A, undergoes anaerobic proteolytic decomposition and the intensity of the luminescent flashes decreases. The steps involved in luminescence in bacteria can be represented as follows:

(A)  $L$  (reversibly oxidized luciferin) +  $XH_2$  (substrate)  $\rightleftharpoons$   $LH_2$  (luciferin) +  $X$

(B)  $A$  (luciferase) +  $LH_2$   $\rightleftharpoons$   $A \cdot LH_2$  (luciferin-luciferase combination)

(C)  $A \cdot LH_2$  +  $\frac{1}{2} O_2 \rightarrow A + L_1$  (irreversibly oxidized luciferin) +  $H_2O + h\nu$

(D)  $A \rightleftharpoons nB$  (proteolytic products).

This hypothetical scheme represents the luciferase proteolysis and the origin of luciferin from oxidation of some of the substrates in the bacterial cell.

Space does not permit a description of the numerous careful studies of bacterial light intensity in relation to oxygen tension, temperature, pressure, radiation, salts, hydrogen-ion concentration, and various respiratory poisons and accelerators. These results together with details concerning the morphology, histology, physiology and use of luminous organs in other luminous forms will be found in two recent publications of the author, a book, "Living Light," Princeton University Press, 328 pp., 1940, and a

Review of Bioluminescence, in the Annual Review of Biochemistry, vol. X, pp. 531-552, 1941. The bibliography of these two publications, together with that in the author's "Nature of Animal Light," J. B. Lippincott, 1920, and "Recent Advances in Bioluminescence," Physiological Reviews, vol. IV, pp. 639-670, 1924 covers the extensive literature of original papers.

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## BIOPHOR

Theoretical smallest particle of living things.

## BIOMETRY

Statistical study of living things.

## BIOPHYSICS, SCOPE, PRINCIPLES, AND METHODS

The domain of discussion may be indicated by defining biophysics as the application to biological research of the methods and content of the physico-mathematical sciences. "Method" is advisedly placed first. It has become clear that the experimental and theoretical procedures usually associated with physics are not the exclusive property of that science, but represent rather adequately the developed and mature form of the scientific method itself. Biophysics is the adaptation of this methodology to the problems of biology.

It appears from this that the word "biophysics" is in part a misnomer. Biophysical research is biological research with a particular emphasis—a concern for the logical ordering and quantification of biological theory, for the more intimate unification of theory and experiment, for the introduction into experimental biology of techniques

and measuring devices which have been developed in the so-called physical sciences, and for the reduction—when it is possible and useful, and only then—of biological problems and concepts to already existent laws and concepts of the physical sciences. Jacques Loeb, a founder of biophysics, certainly devoted most of his efforts to formulating biological problems in terms of presumably underlying physical laws. But when he came to discuss theory, he stressed quantification almost exclusively—he did not assert that biology cannot become a science until it is physical, but that it cannot become a science until it is mathematical.

That physics—the science of matter—has in fact preoccupied itself with those objects which used to be termed “non-living” is logically accidental, not intrinsic. Taken in this sense, the “physicalizing” of biology merely means the attempt to analyze certain complex phenomenal patterns in terms of somewhat simpler patterns which have already been the object of intensive study. In this sense it is neither novelty nor heresy, but an inevitable extension of the classical biological procedure of analyzing organisms into organs, organs into tissues, tissues into cells, and cells finally into their discernible parts.

It is only fair to add that “biophysics” is usually used in a sense which contrasts it with biochemistry—that is, as a study of the physical as distinct from the chemical aspects of biological systems. This viewpoint would see viscosity, osmotic pressure, surface tension, the electrical and mechanical properties of biological systems as physical, while the composition and metabolic activities of such systems

are the concern of chemistry.

This criterion has been serviceable in the past, of course; but it is so narrow as to be both cramping to research and rather difficult rigidly to maintain. Thus, the study of bioluminescence must in this view separate sharply into two parts: the analysis of the luciferin-luciferase system is biochemistry, while the emission of a photon by the reduced enzyme is biophysics. It is valid to say, “For the moment, let us consider only the physical aspects of this phenomenon, and ignore the chemical and purely biological.” But the moment passes quickly, and the essential inseparability of the different aspects demands the broader interpretation.

It remains to consider the best way of subdividing biophysical activity into its branches according to some specified criterion of classification. From the preceding discussion it is clear that one apparently natural division—into theoretical and experimental—is not a desirable one. The nature of biophysics, as here defined, demands the same close interweaving, mutual support, and mutual stimulus of theorizing and experimenting as is now practised so successfully in physics.

To adopt the existing fundamental divisions of biology is no more desirable; for the fences around bacteriology, embryology, histology, physiology, botany, and the like, in view of their haphazard historical origin, exhibit small regard either for practical utility or for logical consistency. Some of these fields are organized around a particular function, some around a particular set of structures, some around a particular class of organisms, and

some are mere catch-alls for topics which do not fit handily into the remaining cells.

If we accept the cell as a fundamental concept in biology, a useful though by no means perfect mode of classification suggests itself—the hierarchy: cell-parts, cells, cell-aggregates. These further subdivide in a fairly natural way, principally according to functions and activities.

Thus, under Cell-parts, we think of: Protoplasmic Structure; Enzyme Systems of the Cell; Nucleus and Chromosomes; Cell Membranes and Permeability; Golgi Bodies and Mitochondria.

Under Cells would come: Growth; Form; Motion; Division; Differentiation; Metabolism; Senescence; Stimulus-Response.

Under Cell-aggregates there are similar categories: Organic Form and Differentiation; Growth; Metabolism; Senescence; Stimulus-Response. These would intersect with the triple classification: Tissues; Organs; Organisms. Thus, for example, we would find Secretion under Metabolism, Organs (perhaps also under Cells, Metabolism); special senses under Stimulus-response, Organs; and the nervous and endocrine systems under Stimulus-response, Organisms. Another category under Cell-aggregates would be Populations, which would cover the material of biometrics, ecology, and much of bacteriology.

Such a topic as The Virus is not an insuperable obstacle to this arrangement; there are many good reasons for placing it under Cell-Parts. But it is obvious from the topics named that a better method

than either equal-ranking classes or a hierarchy would be a multidimensional network, in which topics may be different distances apart, but in which each topic is linked to many others directly, and to all others indirectly. Protoplasmic Structure would be close to if not precisely at the centre of such network. With the further development of biophysics, the appropriate ordering will doubtless become more evident.

Biophysics in the broadest sense, especially on the theoretical side, is not represented with complete adequacy by any one text. One excellent study in phenomenological terms is "Physical Biology," by Alfred Lotka. The tendency to reduce biological problems to molecular-kinetic theory is represented by N. Rashevsky; see "Mathematical Biophysics" and "Advances and Applications of Mathematical Biology." Studies like those of Lotka, but highly abstract, are those of the mathematicians V. Volterra ("Theorie Mathematique de la Lutte pour la Vie") and V. Kostitzin ("Biologie Mathematique"). An attempt to analyze the fundamental concepts of certain fields of biology with logical rigor, but non-mathematically, and which assuredly deserves inclusion, is "The Axiomatic Method in Biology," by Joseph H. Woodger.

At the other extreme are the studies, too numerous even to begin citation, which involve simply the borrowing of apparatus or instruments from physics for use in biological research. Closely related are the use of radioactive isotopes as tracer substances in metabolic studies, of X-ray and other optical techniques for studying the struc-

ture of biologically interesting substances.

Less easy to classify, but definitely biophysical, and usually combining theoretical and experimental work, are such examples as the classical studies of A. V. Hill on muscular contraction, of S. Hecht on vision, and (most recently) of Hoagland in "Pacemakers and Certain Aspects of Behavior."

Applied biophysics is exceedingly scanty. There are a few scattered medical applications, such as the gold number or its modern equivalents in the analysis of cerebrospinal fluid, the use of X-rays and radium in the treatment of cancer. But biophysics is yet too young to show applications on any large scale.

There are many fields of biology in which the rather young biophysical method has not been active, so that a sufficient amount of representative material is not available for presentation. Some topics of biophysical interest, e.g., metabolism, are still referred to biochemistry for the same reason.

JOHN M. REINER.

# BIOPLASM

Germinal cells.

# BIOPSY

Examination of living tissue.

# BIOS

Vitamin necessary for yeast growth; found to be a mixture of i-inositol, vitamin ( $B_1$ ) and "biotin" and/or pantothenic acid.

# BIOS I

I-inositol.

# BIOS II A

Beta-alanine.

# BIOS II B

Biotin.

# BIOSE

A carbohydrate with two carbon atoms.

# BIOSTERIN

A highly active vitamin A concentrate, first prepared in 1925 by Takahashi.

# BIOTIC ENERGY

A mystic term for the processes of life.

# BIOTIN

The term "biotin" should now replace several old names, to wit: coenzyme R (of Allison, Hoover and Burk), protective factor X (of Boas), the protective factor against egg white injury (of Parsons), the vitamin H (of György) and a part of the Bios II b or the adsorbable factor of the yeast growth promoting substance (of Kögl and Tönnis). It was isolated in 1936 by Kögl and Tönnis from the Bios II b factor of yeast as a methyl ester of the empirical composition  $C_{11}H_{18}O_3N_2S$  and having a melting point of  $166^\circ$ - $167^\circ$  when highly purified. Saponification with cold alkali gives free biotin of the empirical composition  $C_{10}H_{16}O_3N_2S$  and melting at  $230^\circ$ - $232^\circ$ . Biotin is a simple monocarboxylic acid, a derivative of valeric acid. The nitrogen atoms form a urea structure which can be opened up with a loss of one carbon to form a diaminocarboxylic acid, from which in turn one can reform biotin by reaction with phosgene. The sulfur is functioning in a thioether structure, since a sulfone can be formed by oxidation. The most probable structure is that of 2'-keto-3,4-imidazolido-2-tetrahydrothiophene-n-valeric acid.

Looked upon as an active principle of yeast growth biotin is active even at a concentration of one part in 500,000,000,000. As the active

substance stimulating several species of the root-nodule bacterium *Rhizobium* and obtained from concentrated cultures of *Azotobacter*, and previously known as coenzyme R (R=respiration) it shows effects in concentration of 1 part in 100 billion. As Vitamin H (H for "Haut" or skin) it counteracts the effects of avidin of both raw and dried egg white to the extent of 10,000 units per milligram by a rat assay method (i.e. 0.1 gamma of biotin per rat per day for 30 days protects against egg-white injury). The biotin may be extracted from liver, dried eggs, potato starch, fresh eggs, dried yeast, autolyzed yeast.

Inactivation of biotin has been accomplished both under acid and alkaline conditions. Aeration is not effective but stronger oxidizing agents destroy activity quickly and completely. Nitrous acid inactivates without a loss of nitrogen.

Biological effects of biotin other than those used in assay of the foregoing effects concern the fatty infiltration of the livers of rats on a low fat diet with high biotin. The fermentation of yeast is increased as well as its respiration and growth both aerobically and anaerobically, in the presence of plentiful nitrogen in the form of ammonia. Butter-yellow tumor formation brought on by avidin-containing diets should be counteracted by biotin.

W. M. M.

#### BIBLIOGRAPHY

- F. Kögl and Tönnes: *Zeit. physiol. Chem.*, 242: 43 (1936).  
 F. E. Allison, S. R. Hoover and D. Burk: *Science*, 78: 217 (1933).  
 V. du Vigneaud, D. B. Melville, P. György and C. S. Rose: *Science*, 92: 62 (1940).  
 M. A. Boas: *Biochem. J.*, 21: 712 (1927).

- P. György, R. Kuhn and E. Lederer: *J. Biol. Chem.*, 131: 734 (1939).  
 P. György, C. S. Rose, K. Hofmann, D. B. Melville and V. du Vigneaud, *Science*, 92: 609 (1940).  
 V. du Vigneaud, J. M. Spangler, D. Burk, C. J. Kensler, K. Sugira and C. P. Rhoads: *Science*, 95: 174 (1942).  
 F. Kögl and Co-workers: *Zeit. physiol. Chem.*, 269: 61, 81 (1941).  
 V. du Vigneaud and Co-workers: *J. Biol. Chem.*, 140: 643, 763 (1941).

#### BIOTIN, ROLE IN PLANTS

See Plant Growth Hormones.

#### BISABOLENE

A sesquiterpene found in many oils.

#### BISEXUAL

Having the essential characters (organs) of both sexes.

#### BLACKMAN REACTION

See Photosynthesis.

#### BIURET REACTION

A general test for a protein or polypeptides containing three or more amino acids; to a solution of the substance tested add a dilute solution of  $\text{CuSO}_4$  and then a dilute solution of sodium hydroxide. A blue-violet color is formed if a long polypeptide is present, and a violet purple color if a short one is present.

#### BLACK'S TEST

A qualitative test for betahydroxybutyric acid.

#### BLASTEMA

Formative substance in an egg.

#### BLASTOCELE

The hollow internal region of the blastula, filled with a colloidal fluid probably exuded from the cells.

#### BLASTOCOLLA

A gummy substance coating certain buds.

#### BLASTOCYST

Germinal cell layer.



**BLASTOGENESIS**

Reproduction by budding.

**BLASTOMERE**

Term applied to a cell forming part of a blastula, the first formed by zygote division.

**BLASTULA**

A single-layered, hollow ball of cells, an early stage of embryonic development, formed from the fertilized egg by cleavage and cell migration.

**BLIGHT**

Withered plant condition due to parasites.

**BLINDNESS, NIGHT**

See Eye, Biochemistry of.

**BLIND SPOT**

Area of retina where optic nerve originates.

**BLOCH DOPA REACTION**

Frozen skin, treated with a 1% dopa solution (3, 4-dihydroxyphenyl alanine), gives rise to a dark brown or black pigment. Reaction due to a specific oxidizing enzyme, dopaoxidase. Used to indicate leukoderma or vitiligo.

Reference: Zeit. physiol. Chem. 98, 226 (1917). Arch. Dermatol. Syphilis 1917, 124.

**BLOOD**

A red fluid, sp. gr. in man 1.055, composed of red and white blood cells, the erythrocytes and leukocytes, suspended in a straw colored liquid, the serum or plasma, dissolved in which are fats, amino acids, carbohydrates, vitamins, hormones, etc. The blood is essential to the transport of  $O_2$  and  $CO_2$  to and from the tissues, the food to the cells, waste products to the excretory organs, etc. The amount of blood is about 9% of the body weight, and contains

between 40—45% of the vol. of the red blood cells.

**BLOOD DIFFERENTIATION TEST**

See Filomusi-Guelfi.

**BLOOD, ACID-BASE BALANCE OF**

The normal pH of the body is 7.4 and the maximum tolerated variations are 0.4 pH units. Blood serves as a buffer medium. It helps the tissues to maintain an acid-base balance by virtue of ventilation and kidney action. Forced respiration may cause enough loss of carbon dioxide to step up the pH 0.2 to 0.3 units. The tissue fluids are considerably stronger buffers than even the blood. About 2/3 of the buffering action of blood against strong acids is carried by bicarbonate. A decrease in the pH and in the alkali reserve stimulates increased ventilation which tends to undo the decrease; an increase in the pH brings about decreased ventilation which tends to undo the increase. The buffer system of the blood is not mathematically the most efficient but has the advantage of working well with easily accessible carbon dioxide and difficultly accessible alkali. Buffering capacity, however, has to be rebuilt by the kidneys. This may occur through the excretion of acid phosphates or the formation of ammonia from urea. A small change in pH of the blood is accompanied by large changes of pH in the urine. Acid urines bespeak the building up of an "alkali reserve" in the blood. Ammonia formation is a secondary defense and leads to the sparing of bicarbonate, e.g. in diabetes, diarrhea with loss of alkali, etc. Excess of bicarbonate is simply taken care of by excretion.



The buffering action of the blood keeps the difference of pH between arterial and venous blood down to 0.02 units. The carbon dioxide is all accounted for as  $\text{HCO}_3$  and  $\text{H}_2\text{CO}_3$ . The buffering action leads to a conception of acidosis not as a condition marked necessarily by a low pH but by an accumulation of a high amount of buffered acid tending to destroy the alkali reserve. Similarly alkalosis need not show directly in the pH. Thus one might ingest a certain amount of strong  $\text{HCl}$  without a material change of pH but at a loss of alkali reserve. An acidosis, e.g. in diabetes, starts a chain of events as the reduction of the ratio of  $\text{HCO}_3$  to  $\text{H}_2\text{CO}_3$ . The  $\text{CO}_2$  has to be reduced and that means increased ventilation. Thus a condition of hyperpnea is set up. This is followed by dyspnea. The urine will be acid because of excretion of ammonium salts. Acidosis may also be due to retention of carbon dioxide for some reason. W. M. M.

#### BLOOD CRYSTALS

Haemoglobin, haemin, etc. crystals formed on shaking blood with ether or chloroform.

#### BLOOD DUST

Droplets of neutral fat in blood.

#### BLOOD PLATELETS

Colorless bodies about 1/3 size of red blood corpuscles.

#### BLOOD REACTION, BIOLOGICAL

See Guyot.

#### BLOOD, RESPIRATORY FUNCTION OF

See Respiration.

#### BLOOD SERUM

Fluid left after removal of corpuscles and fibrin.

#### BLOOD SUGAR, REGULATION OF

Blood sugar is an index of a metabolic process which does not proceed evenly. It is supplied from more than one source and it is utilized at many places. The dynamic balance, therefore, is subject to possible violent fluctuations which are difficult to trace back because of a multiplicity of causes.

From Claude Bernard to F. C. Mann the demonstration has become cumulative that the liver is the prime factor for maintaining the normal blood sugar level. It does so directly from its own glycogen stores and indirectly from muscle glycogen by converting muscle lactic acid to its own glycogen.

Techniques of study have been developed around the study of diabetic animals, so rendered by surgery or by phlorhization, and even more direct demonstrations, demonstrating the formation of liver glycogen not only from glucose but from protein and fat and the hydrolytic products of protein and fat. The concept of the D:N ratio or the ratio of the amount of glucose excreted to the amount of nitrogen excreted, e.g. in a depancreatized or phlorhizinized animal, has been very helpful in studying the changes. The D in this ratio really represents a difference between the hepatic contribution and extra-hepatic utilization. Proper interpretation leads to the conclusion that diabetics utilize carbohydrates quite well and that the entire dietary and hormonal picture must be balanced quantitatively, that ketosis is due to heightened formation of acetone bodies in the liver and not

through failures in the extra-hepatic tissues. Analysis of data on the respiratory quotient (R.Q.) leads to more or less similar conclusions. The breakdown of fatty acids in ways other than at the beta carbon has eased up the arguments for the conversion of fat to glucose. This was further bolstered by direct experiments with animal tissues, such as perfusion of the isolated liver.

Modern research tends to emphasize the role of the liver in maintaining blood sugar levels in balancing out the utilization of the tissues. The contribution of insulin by the pancreas is important, but not all important, because conditions can be set up where one can do fairly well without the pancreas, e.g. the "Houssay" animal, lacking both the anterior pituitary and the pancreas and comparatively free of diabetic symptoms for many weeks. This endocrine balance is not the only one, because the thyroid and the suprarenal cortical hormones are also involved in conjunction with their dependence on the pituitary for stimulation. All these effects, however, are criss-crossed and complicated by hormonal effects on the tissues, if only to a smaller degree under normal conditions, and to a large degree under emergency conditions (e.g. secretion of epinephrine in sudden calls for defense). Many disturbances may be due to overproduction of sugar rather than breakdown in utilization. Similarly "underproduction" is relative to "over-demand." This can only result in finer differentiations of types of disturbances of the homeostatic "mechanisms" for maintaining blood sugar at optimum levels.

References: S. Soskin, *Physiological Reviews* 21, 140-193 (1941).

## BLOOD, TESTS FOR, IN URINE, ETC.

See Adler Benzidine, Adler Leucomalachite, Almén, Bardach, Donogany, Inouye, Van Deen.

## BLOOD TRANSFUSION HUMAN, IMMUNOLOGICAL ASPECTS OF

The presence of isoagglutinins, i.e., antibodies that agglutinate cells of the same species is an important factor in human blood transfusion. Human serum contains two main agglutinins for erythrocytes designated  $\alpha$  and  $\beta$ , while the two agglutinogens occurring in the red cells are A and B. This gives rise to 4 groups of human blood. One group (AB) contains A and B only; another (O) contains only  $\alpha$  and  $\beta$ . A third group (A) contains A and  $\beta$  only, and a fourth group (B) contains B and  $\alpha$  only. Individuals of group AB containing no agglutinins in the serum are sometimes called universal recipients, while individuals of the second group, having no isoagglutinins in the cells are described as universal donors.

## BLOOM

Wax layer on surface of fruits.

## BLOOR'S METHODS FOR FAT ANALYSIS

Colorimetric method for cholesterol (J.B.C. vol. 24, p. 277 (1916); vol. 27, p. 106 (1916); vol. 29, p. 437 (1917).

Phospholipid determination J.B.C. vol. 82, p. 273 (1929).

Lipoid determination by chromate titration (J. B. C. vol. 77, p. 53 (1928).

## BLOXHAM'S TEST

An old qualitative test for urea based on conversion to barium cyanurate.

**BLUBBER**

Whale and seal fat between skin and muscle.

**B. M. R.**

Basal metabolic rate, an average value of consumption of oxygen and production of carbon dioxide under standardized conditions of normal metabolism.

**BODY, COMPOSITION OF**

See Protoplasm.

**BOGOMOLOFF REACTION FOR UROBILIN**

Treatment of an alkaline solution of urobilin with copper sulfate solution gives rise to a red or violet color which may be extracted with chloroform.

Reference: Zentr. med. Wiss. 1875, 210. Deut. med. Wochschr. 1913, 360. Münch. med. Wochschr. 1921, 1558; 1922, 1318.

**BOLLIGER REACTIONS FOR CREATININE**

I. Creatinine, in sodium hydroxide solution, gives a purple with an approximately 10% solution of sodium 3,5-dinitrobenzoate.

II. A pink to rust-brown color, depending upon the creatinine concentration, is obtained when the substance is treated with an aqueous alcoholic solution of 1, 3, 5-trinitrobenzene and dilute sodium hydroxide.

Reference: Med. J. Australia 2, 818 (1936). J. Proc. Roy. Soc. N. S. Wales 69, 224; 70, 211.

**BONANNO'S TEST**

A test for bile pigments.

**BONDI-SCHWARZ TEST FOR ACETOACETIC ACID IN URINE**

Acetoacetic acid decolorizes Lugol's iodine solution, the reaction product having a sharp characteristic odor. This is a modified reaction.

Reference: Wiener klin. Wochschr. 1906, 37.

**BONE**

Part of skeleton tissue hardened by calcium salts, such as calcium phosphate.

**BONE, INFLUENCE OF DIET ON THE COMPOSITION OF**

On reviewing the literature, dealing with the composition of bone, it may be stated that there has been only scant effort to interrelate diet to the composition of bone. It is generally recognized that the inorganic composition of bone may be expressed as  $[\text{Ca}_3(\text{PO}_4)_2]_n\text{-CaCO}_3$ . Where  $n$  is between 2 and  $3^{1-3}$  except that approximately 6 per cent of the Ca is replaced by Mg, Na, and K.<sup>4</sup> It has been known, from a few papers, that  $n$  decreases with age, in high calcium—low phosphorus rickets and in a pathological condition called "Marble bones".<sup>4-6</sup>

In experiments recently reported<sup>7</sup> an attempt was made to interrelate the above findings to the ratios of dietary calcium to phosphorus (which influence the ratios of serum calcium to inorganic phosphorus<sup>8,9</sup>.) It was found that the bones of rats fed high calcium low phosphorus had significantly higher carbonate to phosphate ratios than the group of rats on the high phosphorus low calcium diet.

The rats which received vitamin D supplements had denser bones, but the ratio of carbonate to phosphate in the bones was similar to those animals which did not receive the anti-rachitic vitamin. An examination of the blood revealed that the calcium to inorganic phosphorus ratio was higher of the high calcium-low phosphorus fed rats than the high phosphorus and low

calcium fed animals. In the presence of vitamin D these differences still prevailed but were less marked. The serum Ca x P products, however, was higher explaining the increased density of the bones.

Thus the most important factor in determining whether there was a "high carbonate" bone (low n) or "low carbonate" bone (high n) depended upon the ratio of calcium to phosphorus in the diet. These experiments, therefore, indicate that the dietary calcium to phosphorus ratio has an important influence on the composition of bone.

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#### BIBLIOGRAPHY

<sup>1</sup> Klement, R., *Z. physiol. Chem.*, 196: 140 (1931).

<sup>2</sup> Bogert, L. and Hastings, A. B., *J. Biol. Chem.*, 94: 473 (1931).

<sup>3</sup> Logan, M. A., *Physiol. Rev.*, 20: 522 (1940).

<sup>4</sup> Logan, M. A., *J. Biol. Chem.*, 110: 375 (1935).

<sup>5</sup> Kramer, B. and Shear, M. J., *J. Biol. Chem.*, 79: 147 (1928).

<sup>6</sup> Kramer, B., Yuska, H. and Steiner, M. M., *Am. J. Dis. Child.*, 57: 1044 (1939).

<sup>7</sup> Sobel, A. E., Rockenmacher, M., Weinstein, J. and Kramer, B., presented before the Biological Division, American Chemical Society, Buffalo, New York, September 7-11 (1942).

<sup>8</sup> Kramer, B. and Howland, J., *J. Nutrition*, 5: 39 (1932).

<sup>9</sup> Bethke, R. M., Kick, C. H. and Wilder, O. H., *J. Biol. Chem.*, 98: 389 (1932).

#### BONE SALT

Name sometimes applied to the inorganic matter of bone; essentially  $2\text{Ca}_3(\text{PO}_4)_2 \cdot \text{CaCO}_3$ , i. e. dihalite.

#### BORINSKI TEST FOR PEROXIDASE IN MILK

A bright blue color is obtained when 5 cc. raw milk are mixed

with 10 drops of a solution made by dissolving 0.85 gm. of finely powdered guaiac resin in 85 gm. 75% alcohol, to which is then added 10 cc. liquid phenol and 5 cc. 3% hydrogen peroxide.

Reference: *Zeit. angew. Chem.* 39, 281 (1926).

#### BÖRNSTEIN REACTION FOR SACCHARIN

A yellow color changing to red and then to dark green is obtained when saccharin is heated with excess resorcinol and a few drops of concentrated sulfuric acid. Dilution and addition of excess alkali yields a solution reddish by transmitted light. Sensitive to 1 mg. saccharin in 5-6 liters of water.

Reference: *Zeit. anal. Chem.* 27, 165 (1888); 28, 352, 713 (1889). *Chem.-Ztg.* 267 (1899).

#### BOSE REACTION FOR REDUCING SUGARS

The test solution is added to the reagent which has been heated for less than a minute; a deep violet color indicates reducing sugars. Reagent — 2 cc. 25% sodium carbonate solution mixed with 1 drop of 1% o-dinitrobenzene solution.

Reference: *Zeit. anal. Chem.* 87, 110 (1932).

#### BOTULIN BOTULISM

Allantiasis; poisoning due to a toxin of *B. botulinus*. The toxin, botulin, may be found in meats and vegetables insufficiently cooked. There is a variable period of incubation followed by eye symptoms and motor depression. Antitoxins have been developed but must be used very early. Botulin is so powerful that mere tasting of spoiled food may be fatal, yet it is destroyed

by boiling for several minutes.  
See also Microbiology.

**BOUMAN REAGENT FOR INDICAN IN URINE**

Indican in urine is estimated using a solution of 20 mg. isatin in 1000 cc. of iron-free hydrochloric acid. Zeit. physiol. Chem. 32, 82.

**BOVIDAE**

The family of ruminants.

**BOYLE'S LAW**

The volume of a fixed mass of a given gas at constant temperature is inversely proportional to the pressure.

**BRADSHAW TEST FOR MYELOPATHIC ALBUMOSE IN URINE**

Presence of Bence-Jones protein-myelopathic albumose — is indicated by the formation of a precipitate when concentrated nitric acid is added to cold urine. Precipitate dissolves on heating and reprecipitates on cooling, in contrast to ordinary albumin.

Reference: Brit. Med. J. 1906, 11, 1442.

**BRANCHIAE**

Gills.

**BRAZILIN**

Brasilin;  $C_{16}H_{14}O_5$ ; an amber-colored flavone from Brazil wood; used as an indicator.

**BREAD MOLDS**

See Microbiology.

**BREATHING**

See Respiration.

**BREADFRUIT**

Fruit of *Artocarpus* (Polynesian) tree.

**BREECH**

Buttocks.

**BREED**

A race variety.

**BRIEGER REACTION FOR DIFFERENTIATING CHOLINE AND NEURINE**

With phosphotungstic acid, choline but not neurine will precipitate; with tannic acid, neurine but not choline will precipitate.

Reference: Brieger, Ueber Pto-  
maine, 1885, Berlin.

**BRIOLOGY**

Science of mosses; muscology.

**BRIGHT'S DISEASE**

Nephritis; nephrosis; a term for a set of kidney disorders with inflammatory and degenerative lesions. Nephritis stresses inflammation of the kidneys, while nephrosis stresses the degenerative changes. Vascular changes may be called sclerosis. The main groupings are (1) acute glomerulonephritis (2) the nephroses (lipoid nephrosis, chronic parenchymatous nephritis and sub-acute nephritis with edema) and (3) the nephroscleroses (chronic nephritis and chronic interstitial nephritis). In acute glomerulonephritis infection, such as by hemolytic streptococci, is primarily responsible. Albumin in the urine, fever, edema may lead to hypertension, uremia or cerebral hemorrhage. Various forms of albuminuria have been differentiated to aid diagnosis of nephritis. Persistence of high-blood urea nitrogen indicates great kidney damage. Diets emphasize carbohydrate and fat. Diuretics of increasing power are used cautiously. The nephroses involve degeneration to necrosis of the parenchyma of the kidney with respect to albumen, fat, lipoid or carbohydrate. There is marked albuminuria and hypoproteinemia. Infections and poisoning, e.g. by

mercury, are possible causes. There are symptoms of edema all over the body, digestive, circulatory, urinary and uremic symptoms. The blood shows hypercholesterolemia, a reversal of albumin to globulin ratio, an increase in sodium chloride, a diminution of total protein. A decrease in basal metabolism also takes place. The edema is difficult to remove by diuresis or diaphoresis, but this can be accomplished by raising the colloid-osmotic pressure by intravenous injection of acacia or by increased protein intake. The nephroscleroses are due to pathological changes in the vascular and interstitial tissues with symptoms of albuminuria, hypertension, edema, nitrogen retention, acidosis and uremia. The disease is preventable but hardly curable. Heart therapy is stressed.

Many tests have been developed in connection with Bright's disease, as tests for albumin and blood in the urine (see benzidine test), kidney function tests (see phenolsulfonephthalein test, Volhard's concentration and dilution test, urea clearance test), blood chemistry tests such as N.P.N. (non-protein nitrogen or urea nitrogen) bilirubin, calcium, icteric index, serum albumin and globulin, total protein, van den Bergh, uric acid, carbon dioxide combining power, chlorides, cholesterol and cholesterol esters, xanthoproteic test for phenol.

#### **BROM-CLARK METHOD**

See Ergot.

#### **BROMELIN**

An intracellular proteolytic enzyme found in the pineapple. It is similar in action to papain.

#### **BROMIDROSIS**

The unpleasant odor of perspiration due to rancidity of fatty constituents.

#### **BROMURAL**

Alpha-bromoisovaleryl urea, a sedative and hypnotic; "dormigene."

#### **BRONCHIOLES**

See Respiration.

#### **BRONCHOCELE**

See Goiter.

#### **BRONCHUS** (pl. bronchi)

Branching tube connecting trachea with lungs.

#### **BROWNIAN MOVEMENT**

Rapid, random, oscillatory movement around a mean position, executed by any particle of small enough size to remain in more or less permanent suspension in a liquid; the result of the random impacts of molecules of the liquid upon the particle.

#### **BROWN-LUM REACTION FOR DIFFERENTIATING**

##### **DEXTROSE AND LEVULOSE**

Ferric chloride solution is added dropwise to a solution of 0.5 gm. of the sugar in 10 cc. water until a permanent yellow is obtained. On warming, a slightly deeper color is formed with levulose; the solution is colorless with dextrose. On addition of 1 drop of 2% diphenylamine in sulfuric acid, an intense violet indicates levulose.

Reference: Pharm. J. 131, 63 (1933).

#### **BRUCELLERGEN**

See Brucellosis.

#### **BRUCELLOSIS**

Undulant fever; Malta fever; an infection caused by one of the *Brucella*, e.g. *Brucella melitensis* (goats), *Brucella abortus* (cows), *Brucella suis* (hogs) via milk or



through the skin after a period of incubation. Fever symptoms may be supplemented by many others. A brucellergen skin test, based on a nucleoprotein of *Brucella*, is diagnostic. Agglutination and opsonic tests, as well as cultivation of the organism from the blood, are used. Vaccines are available for treatment.

#### BRUCINE

An alkaloid found with strychnine; dimethoxystychnine; less poisonous than strychnine;  $C_{23}H_{28}O_4N_2$ .

#### BRUECKNER TEST FOR ERGOSTEROL

A solution of the substance in 2 cc. of benzene or chloroform is treated with 1 cc. acetic anhydride, 0.5 cc. acetone, a small crystal of copper acetate and 0.5-1 gm. anhydrous zinc chloride. A blue-violet color with reddish fluorescence is obtained. Sensitivity — 0.001 mg. per cc.

Reference: *Biochem. Zeit.* 270, 346 (19434).

#### BRUGSCH TEST FOR PORPHYRIN IN URINE

Acidify 10 cc. of urine with 2 cc. glacial acetic acid, extract with 2 cc. ether; treat ether extract with 5 cc. 5% hydrochloric acid and shake thoroughly. Viewed under ultra-violet light, a red fluorescence is obtained with porphyrin.

Reference: *Münch. med. Wochschr.* 81, 1546 (1934).

#### BRUNNER'S GLANDS

Glands in submucous coat of small intestine; duodenal glands.

#### BRYOLOGY

See Briology.

#### BRYOZOA

Sea-mosses.

#### BUCCAL

Referring to the mouth or cheeks.

#### BUD, ADVENTITIOUS

A bud not from the stem apex or axil of leaf.

#### BUELOW TEST FOR ACETONE IN URINE

Acetone reacts very rapidly at room temperature with a hydrochloric acid solution of 2,4-dinitrophenylhydrazine to form a precipitate. The test is quantitative and will detect as little as 0.1%.

Reference: *Klin. Wochschr.* 4, 428 (1925). *Pharm. Ztg.* 71, 428 (1926).

#### BUFFER

Substances, which by their presence in solution increase the amount of acid or alkali that must be added to cause unit change in pH; the most efficient buffers are mixtures of weak acids or weak bases with their corresponding salts.

See also Blood, Acid-Base Balance of.

#### BUFODESOXYCHOLIC ACID

A compound of bufotalin and suberyl arginine;  $C_{40}H_{62}O_{11}N_4$ .

#### BUFOTALIN

A sterol-like compound found in toad venom;  $C_{28}H_{36}O_6$ .

#### BUFOTOXIN

Active principle of toad venom; a compound of bufotalin and suberyl arginine;  $C_{40}H_{62}O_{11}N_4$ .

#### BUFFER INDEX

See B. I.

#### BULBOCAPNINE

$C_{19}H_{19}O_4N$ ; rhombic needles, m. p.  $199^\circ$ ; alkaloid of several genera of *Corydalis* and *Dicentra*; it is a benzanthrane derivative; stimulates flow of saliva and tears, produces emesis, slows respira-

tion, and produces a cataleptic condition.

# **BULLOCK**

Castrated bull.

# **BURCHARD REACTION FOR CHOLESTEROL**

The addition of acetic anhydride and a few drops of sulfuric acid to a solution of cholesterol in chloroform, chlorobenzene, chlorotoluene or ethylene chloride produces a red to violet color, the acid showing a green fluorescence.

Münch. med. Wochschr. 1913, Reference: Diss. Rostock (1889). 1776.

# **BURIAN REACTION FOR XANTHINE BASES**

Alkaline solutions of adenine, guanine, hypoxanthine and xanthine produce a red color with diazobenzene sulfonic acid. Except for caffeine, heteroxanthine, paraxanthine and theobromine, all methylxanthines react similarly.

Reference: Ber. 1904, 696. Zeit. physiol. Chem. 43, 501; 51, 425.

# **BURSITIS**

An inflammation of a bursa due to trauma or strain or infection,

accompanied by pain when a joint is moved. Special forms have the special names: miner's elbow, tennis elbow, housemaid's knee, weaver's bottom, barge-man's bottom, Fleischmann's bursitis (sublingual), plantar bursitis (over instep), bunion, Albert's disease (foot). Besides casual therapy, injections of sodium morrhuate have been used. Physiotherapy, e.g. heat and massage, is helpful.

# **BUTTER YELLOW**

See Carcinogenesis by Nitrogen-Containing Compounds.

# **BUTYN**

Dibutyl-aminopropyl-p-aminobenzoate sulfate, m.p. 98-100°, local anesthetic used in infiltration anesthesia, rhinology, urogenital surgery, tooth extraction, etc.

# **γ-BUTYROBETAINE**

A nitrogenous base found in teleosts, molluscs and coelenterates.

# **BYSSUS**

Viscous threads whereby mussels attach themselves to objects.

## C

### CACHEXIA

Emaciation due to wasting or malnutrition, cancer, or the like.

### CACODYLATE TEST

See Schulz.

### CADAVERINE

$\text{NH}_2(\text{CH}_2)_5\text{NH}_2$ ; an amine produced by the putrefactive action of bacteria on lysine or proteins containing it.

### CADININE

A sesquiterpene, the main component of oil of cubeb and of cade;  $\text{C}_{15}\text{H}_{24}$ .

### CAECUM

Blind sac into which the appendix opens.

### CAFFEINE

Theine, guaranine, methyltheobromine, trimethylxanthine; m.p.,  $235-237^\circ$ ; sublimes,  $178^\circ$ ; is a weak base; from tea, coffee, guarana, kola nuts; used as diuretic; cardiac, respiratory, vasomotor, reflex, and psychic stimulant; in small doses stimulates muscular contraction and lessens fatigues, large doses having opposite effect.

### CAFFEINE TESTS

See Archetti, Stroup, Wagenaar, Winkler.

### CAISSON DISEASE

The bends; compressed-air disease; divers' paralysis; a condition due to too rapid return from pressures about 32 lbs. per square inch to atmospheric pressure which causes too rapid an evolution of gas from tissues. The gas is principally nitrogen. The pain is referred to as "bends," the vertigo as "staggers" and the dyspnea as "the chokes." Treatment is by recompression.

### CALAMUS

(1) Part of brain; (2) species of palm.

### CALCANEUS

Heel-bone.

### CALCIFEROL

A vitamin D, namely Vitamin  $\text{D}_2$ ; it is a crystalline material, m.p.  $115-117^\circ$ , made by irradiation of ergosterol. It is found in yeast, several fish oils, but not cod-liver oil, and is used in several commercial antirachitic preparations. It contains 3 rings and 4 double bonds.

See Radiation, Biological Effects of.

### CALCIFICATION

Deposition of insoluble calcium salts.

### CALCIUM METABOLISM

See also Teeth, Biochemistry of.

**CALCIUM-PHOSPHORUS  
RATIO, DIETARY**

See Bone, Influence of Diet on.

**CALCIUM TEST FOR**

See Kisser.

**CALCULI, URINARY**

See Urology.

**CALCULUS**

A "stone" in an organ.

**GALEEN**

Whalebone.

**CALLAN-HENDERSON  
REAGENT FOR COPPER**

Copper salts produce a brownish-yellow color when treated with an amyl or isoamyl alcohol solution of sodium diethyldithiocarbamate. Reference: Analyst 54, 650 (1929). J. Biol. Chem. 93, 48 (1931). Biochem. J. 26, 1022 (1932). Analyst, 57, 495 (1932). J. Marine Biol. Assoc. United Kingdom 18, 193 (1932); 19, 63 (1933). J.A.C.S. 55, 4524 (1933). Ann. chim. anal. chim. applic. 17, 145 (1935).

**CALLOSE**

Extraneous material in cell wall, not cellulose.

**CALORIGENIC ACTION**

See Specific Dynamic Action.

**CALLUS**

New bony tissue; scar tissue.

**CALOMEL**

Mercurous chloride.

**CALOMEL ELECTRODE,  
NORMAL**

A half-cell, composed of a layer of mercury-calomel paste moistened with N KCl solution, over which is a normal solution of KCl and saturated with salomel. An electrode of Pt in a glass rod dips into the mercury and leads out of the cell. It is a standard reference cell used as a standard against

which, other half cells are compared.

**CALORIE, GREAT**

Kilogram calorie; food calorie; 1000 small calories.

See Calory.

**CALORIGENIC EFFECT**

Increase of animal's heat production resulting from intake of food or drugs. M. K.

**CALORIMETRY**

The measurement of heat exchange.

**CALORIMETRY, DIRECT**

The measurement of an organism's heat loss by radiation, convection, conduction, and evaporation. M. K.

**CALORIMETER**

An instrument for measuring total heat liberated or absorbed. Unit of standard metabolic rate (See standard metabolism) in kilocalories per day.

**CALORIMETRY, INDIRECT**

Calculation of an organism's heat production based on chemical measurements, mainly of oxygen consumption, or carbon dioxide production or both with or without consideration of urinary nitrogen. M. K.

**CALORY**

Calorie; amount of heat which increases the temperature of one gram of water one degree Centigrade (averaged between the freezing and boiling points of water).

**CALVARIUM**

Dome of skull.

**CAMBIUM**

Soft formative middle layer of a tree.

**CAMBIUM, ACTIVATION OF**

See Plant Growth Hormones.

**CAMBRIAN ERA**

See Paleozoic.

**CAMPBELL TEST FOR DIHYDROXYACETONE**

Dihydroxyacetone reduces phosphomolybdic acid with the formation of a blue color which may be compared colorimetrically or titrated with 0.01 N potassium permanganate to the disappearance of the blue color.

Reference: J. Biol. Chem. 67, 59 (1926).

**CAMPHENE**

$C_{10}H_{18}$ ; present in l-form in citronella, and in d-form in ginger.

**CAMPHOR**

$C_{10}H_{16}O$ ; constituent of camphor tree and laurel.

**CANADA BALSAM**

Oleoresin of the pine *Abies balsamea*; a solution in xylene is used for slide mountings.

**CANALINE**

Amino acid formed from canavanine by a liver enzyme.

**CANANGA OIL**

See Ylang Ylang Oil.

**CANAVANINE**

An amino acid of jackbean.

**CANCER**

See also Growth.

**CANCER AND ESTROGENS**

See Estrogens, Synthetic.

**CANCER METABOLISM**

See Creatine and Creatinine Metabolism.

**CANDLE FOOT**

Intensity of illumination of distance of 1 foot by a standard light.

**CANE SUGAR**

See Sucrose.

**CANTHARIDIN**

Active principle of Spanish (and Chinese) fly; used to stimulate hair growth and to blister skin; alleged to act as aphrodisiac.

**CAPILLARY**

Minute blood vessel connecting an artery to a vein.

**CAPILLUS**

See Hair.

**CAPON UNIT**

The dose of androgenic material which on subcutaneous injection daily for 6 days into at least 5 capons, produces an average increase of 20% in the area of the combs.

**CAPRIC ACID**

n-Decylic acid; occurs as K salt in wool, and as glyceride in milk and vegetable oil.

**CAPROIC ACID**

n-Hexoic acid; occurs as glyceride especially in goat milk.

**CAPRYLIC ACID**

n-Octoic acid; occurs in goat milk, also in free form in sweat.

**CAPSANTHIN**

See Carotenoids.

**CAPSICUM**

Dried ripe fruits of *Capsicum* minimum, used as digestive stimulant or for drawing blood to skin; the active principle is the pungent "capsaicin".

**CAPSORUBIN**

See Carotenoids.

**CAPSULE**

Part of brain; enclosing sac.

**CARBAMIC ACID TEST**

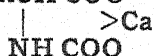
See Abel-Drechsel.

**CARBAMIDE**

Urea.

## CARBAMINO REACTION

The reaction between amino acids, carbon dioxide, barium or calcium hydroxide. Salts of carbamino acids  $\text{RCH COO}$



## CARBARSONE

See Chemotherapy.

## CARBHEMOGLOBIN

A compound said to be formed of about the 5-10% of the total carbon dioxide of the blood which is not bicarbonate but combined with hemoglobin.

## CARBOHYDRASES

A large group of enzymes that hydrolyzes di-, tri-, and polysaccharides to monosaccharides.

R. D. C.

## CARBOHYDRATE AND FAT CATABOLISM AND THEIR RECIPROCAL INTEGRATION

The biochemistry of the catabolism of carbohydrate and of fat,<sup>1</sup> when viewed separately, do not present undue difficulties, but when they must be viewed simultaneously, as linked in a reciprocal manner, and as a part of the "steady state" of normal metabolism, the difficulties are greatly increased. These difficulties are due in part to the fact that these two distinct catabolisms are if anything too well understood for carbohydrate, and at the same time too little understood for fat, to permit an easy and comparable simultaneous view of the two processes. Thus these subjects tend to fall apart in our minds when they should be, as a matter of fact, closely integrated. As in all such situations involving complex relations, we may wisely use the historical approach at first, wher-

ever possible, and thus secure some definite over-all views, where a "close-up" without such a preliminary view would be confusing.

Viewed in this way the reciprocal integration of these two catabolisms is easily established. From ancient times man has known from observations on himself and on animals, that foods other than fatty ones protect the visible reserve of fat in the subcutaneous tissues. During illness or starvation he could see these reserves shrink visibly, and although he could not characterize the substances involved chemically, in a way that would be satisfactory to us, he nevertheless had a realization that these fatty reserves were produced and maintained by an abundance of feeding in times of plenty, and that they were then consumed in times of illness and starvation. Such a remote and over-all reciprocal integration, which is also equally a reciprocal separation, would probably be granted as true by every student of oxidative catabolism.

However, beginning especially with the work of Lavoisier and continuing to the present, studies of animal calorimetry have shown that other things being equal, the combustion of fuel, carbohydrate and fat primarily, takes place on a controlled basis, i.e. on a supply and demand basis, and that we do not have two separate uncontrolled "conflagrations" in our tissues. This raises the question as to how such a control can be achieved.

Here the recently acquired understanding of carbohydrate oxidation in organisms can help us. According to the Wieland theory, and its developments, the potential energy of carbohydrate in catabolism is



largely mediated or transferred as labile acceptor hydrogen, the "gaseous" tension of which is controlled in the living cell by its attachment to acceptors or carriers, so that, although the cell usually shows the definite reducing potential required for such hydrogen, by tests that seem valid, this potential is at the same time nearly balanced by the opposing potential due to oxygen also present and similarly bound to carriers, namely hemoglobin and related compounds. The essential act of control in oxidative catabolism would then in this situation appear as a catabolic "bottle-neck" that determines the rate at which these two components are brought to react to form water. The metabolic hydrogen would thus be the "fuel of life," par excellence, and physiological oxidation would be an "oxygen flame" in a "thin" atmosphere of hydrogen, because the latter is only slightly more abundant than the former. In the first stages of catabolism the metabolites would be passed through a suitable "converter" for their conversion into a uniform fuel, namely metabolic hydrogen, and each converter would produce this metabolic hydrogen on a supply and demand basis according to its capacity to function under the prevailing conditions. The Krebs citric acid cycle, regardless of whether it eventually stands or falls, may be viewed as such a converter, and in this connection is chiefly interesting because it constitutes an example of the metabolic hydrogen generator required. The reciprocal control of the two catabolisms could then be obtained through the relations between the "gas pressures," i.e. the redox potentials attained by the two catabolisms when viewed separately. Thus when much carbo-

hydrate is utilized not much fat would be converted into such hydrogen, but as this was used up more and more, the conditions would be more favorable for fat to furnish a larger share of the converted fuel. In this way obedience to the law of the conservation of energy and the mass action law would be provided for in this "device" for maintaining the "steady state" of the organisms, while making a radical change to a different type of primary fuel.

Such ideas as are expressed in the preceding paragraph are interesting if they can be made to coincide with many known facts. Viewed in this way fat is seen as a "pinch-hitting" hydrogen donor, primarily useful when sugar is not available, and this coincides with the over-all physiological observations mentioned above. It also coincides with the fact that there is apparently no metabolic disease involving fats analogous to that involving carbohydrate as in diabetes mellitus. The sick, it appears, can always utilize the fat available in their body fluids and tissues.

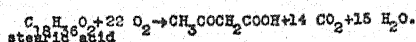
But here we encounter a difficulty arising from the fact that in vitro carbohydrates are comparatively easily burned in aqueous media in comparison with fats, whereas the diabetic whose ability to burn sugar is seriously impaired, can still burn fat with ease, which in aqueous media is extremely difficult to burn. This is the chemical paradox in these two catabolisms that was first clearly visualized about fifty years ago. The subject has had an arduous history since then, and although much was learned, the diabetic really got his first great help from science when insulin was prepared about twenty years ago.

In a similar way, once it became

possible to deal with fats and carbohydrates chemically, and diet studies could be made, it was learned that there is a similar reciprocal relation between the formation of body fat and the consumption of digestible carbohydrate. Thus in the hog, carbohydrate fed in excess of metabolic needs is converted progressively into fat in the production of pork fat. Thus the full picture shows an even more intricate integration. Overfeeding of carbohydrate does not promote overwhelming excessive oxidation of carbohydrate beyond the needs of the body, but the excess is converted into fat. If, however, the feeding is reduced fat formation is reduced, until as carbohydrate available becomes inadequate for the energy requirements more and more fat is burned. Thus carbohydrates not only spare the burning fat, but they may under other conditions actually give rise to fat.

Now although these two catabolisms are separated in this way it was also learned about fifty years ago that they are closely linked in another way. When too large a proportion of fat in relation to carbohydrate is being burned in man the acetone bodies make their appearance in the urine. This ketonuria increases as the carbohydrate combustion is diminished, and becomes a critical matter in uncontrolled severe diabetes. The three compounds involved constitute the unburned terminal fragment of the fatty acid molecule, if we accept the Knoop theory of  $\beta$ -oxidation of fatty acids, in its older traditional form.

That is, in this instance, about seven ninths of the molecule is completely and "safely" burned in



some way, and likewise about seven ninths of the potential energy of the stearic acid molecule is converted. The tragedy of the diabetic patient is that he can do so well on the whole, and yet come to grief on a mere remnant of two ninths of the fatty acid molecule.

Moreover, it was also learned that if carbohydrate catabolism is restored the acetone bodies disappear. This effect is so striking that by about 1905 Rosenfeld could state the situation in the aphorism: "The fats burn (completely) only in the fire of the carbohydrates." As a summary and chemical figurative statement this is still useful as a basis of departure for an explanation, and for the rationalization of dietary management. Moreover, this detail is so important that no matter how acceptable the general ideas expressed above may be for an over-all view, they must take account of and provide for this detail. To deal with this we are obliged to consider the details of these two catabolisms more closely.

**The Catabolism of Carbohydrate**  
The essential facts of this can be briefly stated. In man in the state of rest about half of the oxidative metabolism takes place in muscle, largely at the expense of glycogen, as can be shown by the respiratory quotient when taken under favorable conditions. Here normally the formation of the required muscle glycogen is associated with a favorable insulin relation. The oxidative breakdown is initiated by a double phosphorylation of the glucose unit derived from the glycogen. The ester so formed splits into two triose ester molecules, and it is the

subsequent history of these that results in its further labilization in the form of acceptor of metabolic hydrogen, and that leads either to the hydrogenation of pyruvic acid with the formation of lactic acid, as in the anaerobic catabolism, or to the hydrogenation of oxygen with the formation of water, as in the aerobic process.

The essential steps in the above process can be visualized in *in vitro* conditions. Thus a glucose solution pre-treated with alkali and then neutralized develops properties analogous to those of the triose esters above, and takes up oxygen from the air. It gives reduction tests in the cold. The solution contains so much labile hydrogen that it will reduce methylene blue and similar dyes to their leuco- or hydrogenated forms. The body of the solution containing methylene blue is colorless, while the surface is blue. Diffusion currents carry the blue dye down into the solution where it is promptly decolorized, i.e. reduced, thus showing that there is no available oxygen in the body of the solution. This condition persists until the hydrogen is used up aerobically by being brought to the surface by leuco-methylene blue, or is used up anaerobically in rearrangements within and between the labile molecules in the solution, of which the well known Cannizzaro reaction is the most familiar type.

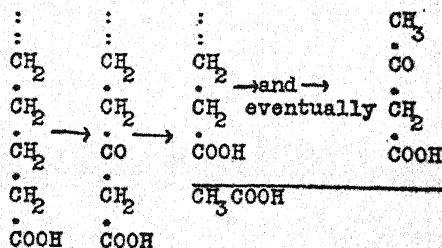
#### The Catabolism of Fatty Acids

In contrast to the above typical and abundant type of carbohydrate breakdown, the catabolism of fats and fatty acids is obscure.

In the first place the reserve fats are laid down in fat depots, where they are segregated in regions that have a comparatively poor blood supply, and in the form of the most

insoluble water-repellant substances abundantly present in the body—namely as neutral fat. Leathes long ago, and Bloor more recently, emphasized this fact, and showed that such fat is mobilized as the half-soluble water-attracting phospholipids of the lecithin type. Moreover, the cholesterol-cholic acid types of fatty esters, besides neutral fat and fatty acids, are to be found in the blood. Taken together such fatty derivatives are several times as abundant as is glucose normally, although this fact is not often mentioned. Such fatty derivatives are also taken to the liver where they are desaturated in part. Their subsequent fate is described in two radically different ways.

(a) One group would assert that the fats undergo oxidative disassembly in the liver in accordance with some form of the Knoop  $\beta$ -oxidation theory. A great deal of work supports the idea that the liver does have a unique role in handling fats both in their original absorption from the bowel, and their manipulation at subsequent stages, but nothing in general physiology indicates that other cells, including organisms without livers, can not utilize fat and fatty acids. However this group would have us believe that in man, for instance, this function of fat utilization and conversion is restricted to the liver, and the essential steps are represented as follows:



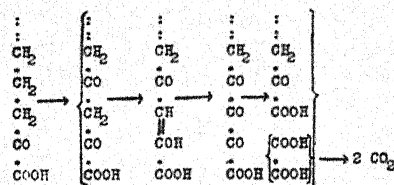
(Acetic acid or some equivalent substance is dropped off that is transported to the site of oxidation.)

There are many variants of this idea, the most significant of which are perhaps that the alternate oxidation proceeds up the chain faster than the removal of the two-carbon residues, and also that four carbon residues of acetoacetic acid may be dropped off at times as well. Some of the possible details of such alternative mechanisms are presented in the essay referred to above<sup>1</sup> and will not be repeated here.

(b) The other group would not minimize the importance of all of the variations of the Knoop theory, but would not restrict fat catabolism to the liver, nor to this one particular type of mechanism. The Knoop theory is established, and rests on the biochemical results obtained in the breakdown of phenyl-substituted fatty acids, and the observation of Dakin that the acetone bodies are formed in the oxidation of butyric acid with hydrogen peroxide. The fact that in Dakin's experiments oxidation also took place on the  $\alpha$ -carbon atom was disregarded later, although reported by Dakin at the time. This willful oversight arose from an error in organic chemistry, made many years ago and known as Popff's Rule,<sup>2</sup> to the effect that if oxidation is initiated on the  $\alpha$ -carbon atom of a fatty chain further oxidation leads to the loss of but one carbon atom. Since fatty acids with an odd number of carbon atoms do not occur in significant amounts in natural fats, this type of oxidation could be excluded. This rule must now be amended to the extent that it is true only under certain circumstances, so far not often found in organisms. More recently the writer

established that initial oxidation of the  $\alpha$ -carbon atom also preferably led to the loss of two carbon atoms from the chain in *in vitro* oxidations. These two terminal carbon atoms could be recovered in one piece, thus proving that they had indeed been removed in one fragment, which by the way has never been established directly for the traditional  $\beta$ -oxidation theory. The alternative mechanism of reaction thus established would in essence constitute an alternative  $\beta$ -oxidation theory based on initiation of oxidation on the  $\alpha$ -carbon atom, and is called the  $\alpha$ -oxidation mechanism. This too was briefly discussed in the essay referred to,<sup>1</sup> and provides an interesting alternative mode of initiation of oxidation, which does not violate any ascertained facts as those established by Knopp and Dakin, and yet provides a highly reactive intermediate for the continuation and completion of the oxidation of the fatty acid molecule.

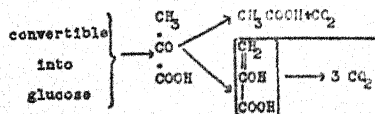
It is obvious that here too the oxidation of alternate carbon atoms may move up the chain in advance of the removal of the two carbon atoms that are to be dropped. This may be visualized as follows:



The oxalic acid may then be obtained as such *in vitro*, but the other stages under the brackets are essentially conjectural, and such evidence as exists for their formation can not be presented here. However, it is evident, that the stages provided would represent

highly unstable compounds, and that so far as ease of oxidation is concerned they would be comparable to the labile sugar derivatives, and at the same time very different, because their reactivity would as represented not be dependent on phosphorylation. This provision might serve to allow such oxidative mechanisms to exist even when circumstances for phosphorylation of carbohydrate derivatives appear to be unfavorable as in diabetes.

The first product,  $\alpha$ -ketobutyric acid, could at times be oxidized completely to carbon dioxide and at other times lose one carbon atom, giving rise to pyruvic acid, and this in turn could be oxidized by some reaction mechanism like the following:



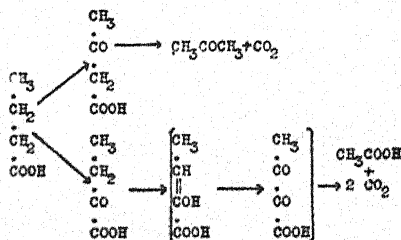
That is to say we may have a traditional  $\alpha$ -oxidation to acetic acid and carbon dioxide, or a complete conversion into carbon dioxide. On the left we have also indicated how this product derived from a fatty acid could give rise to sugar. Similarly such  $\alpha$ -keto acids could be aminated and converted into amino acids, and this could give this  $\alpha$ -oxidation mechanism importance in amino acid synthesis.

In this connection it must be recalled that Knoop has recently been quoted<sup>3</sup> as saying, "pyruvic acid represents, in fact, the great cross-road of the main-metabolic processes, not only between oxidation and fermentation, but also between fat and carbohydrate metabolism." Here we have glimpsed such a cross-road relation and we shall

deal with this from another standpoint later.

This  $\alpha$ -oxidation mechanism for fatty acids can be viewed in various ways, and is only partially considered here.

The Simultaneous Catabolism of Fats by the  $\beta$ - and  $\alpha$ -Oxidation Mechanisms. In Dakin's original observations substantial portions of the butyric acid molecules were attacked according to both of these mechanisms. Subsequently it could be established that,<sup>4</sup> when an alkali phosphate mixture was used as the catalyst, about half was oxidized by either mechanism thus:



It is the writer's opinion that the resistance of acetoacetic acid to oxidation is associated with the difficulty of forming the enol, and that, on the other hand, the ease of oxidation of  $\alpha$ -ketobutyric acid is associated with its facility of enolization. This is an inference drawn from existing information, and so far has not been directly proved. In any case the end-products of  $\beta$ -oxidation, acetoacetic acid and acetone, are only slowly oxidized in this system, while the end-product of  $\alpha$ -oxidation, acetic acid, is also only slowly oxidized. Thus the survival of these substances reveals the nature of the intermediate events.

On the basis of such studies, it is assumed that both mechanisms

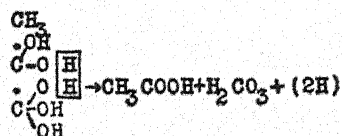


also exist under physiological conditions, and that grossly considered the one accounts in part for the appearance of the acetone bodies when they appear, and that the second mechanism in part accounts for their non-appearance. It is also assumed for the present that in general the two mechanisms will each account for about half of the fat burned, although this may be untrue, especially in certain tissues and at certain times.

This provides for a highly flexible fat catabolism, as contrasted with the somewhat rigid glucose-glycogen catabolism, and in this respect conforms with the flexible "pinch-hitting" quality of fat formation and breakdown, as described above.

In what manner the intermediate mono-, di-, and poly-keto acids provided for are broken down is not known, even in *in vitro* conditions. They are virtually, or in fact, mostly inaccessible substances, because of their instability. Whether, and in what degree, these intermediate keto acids undergo hydrolytic breakdown at a keto group with the formation of a short chain acid, as is generally assumed to occur with acetoacetic acid, for instance,  $\text{CH}_3\text{COCH}_2\text{COOH} \rightarrow 2\text{CH}_3\text{COOH}$ , is entirely unknown. Thus, for instance, the reaction just represented requires a high degree of alkalinity for accomplishment *in vitro*, and an enzyme for its accomplishment is scarcely known at present.<sup>5</sup> However, by visualizing the formation of polyketo derivatives as shown for the second scheme above the oxidation could be completed without the intermediate formation of acetic acid, or a similar compound, each time that two carbon atoms are lost. However, even in such a mechanism the details are also quite

unknown, except in the special circumstance in which oxalic acid is obtained. To conclude that because oxalic acid is obtained in one instance it must always be obtained is so far not justified. Thus even for the *in vitro* oxidation the intermediate stages present serious difficulties. Some of these difficulties may arise from our faulty manner of viewing these things. We have been accustomed so long to considering vital oxidation as a flame in oxygen, and as we have seen above it should more likely be considered to be an "oxygen flame" in "hydrogen." Thus when we speak of fat oxidation we should perhaps speak of fat dehydrogenation. This could of course only occur after a preliminary addition of water, and could be illustrated for pyruvic acid thus:



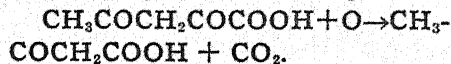
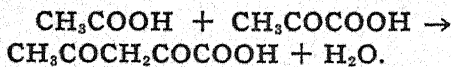
Finally, however, in either type of mechanism we may obtain short chain products, i.e. at least the residual piece of the hydrocarbon chain—acetoacetic and acetic acids, respectively. Such products are freely soluble and could dialyse out of the oxidation system in a way that their parent substances, the long chain fatty acids, could not do. Moreover, in chemical conditions they are quite resistant to oxidation. However, such molecules are known to be readily utilized in the organism under suitable conditions. This could readily be accounted for by allowing them to undergo condensation, by what has been called the "recapture" synthesis, and in such a way that



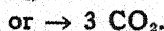
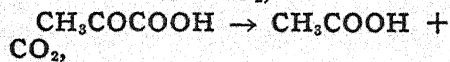
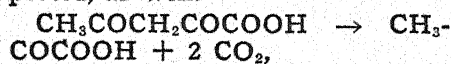
the product formed would be quite susceptible to oxidation.

**The Recapture Synthesis.** One of the most surprising properties of living organisms, after we have visualized their digestive powers, is their power to synthesize kinetically active, diffusible, dialysable molecules into appropriate complexes. Thus it would not be surprising to see the organism recapture an inert and useless molecule and put it into a place where it becomes active and important. Perhaps the most spectacular instance of this sort is the conversion of the physiologically inert glucose of the blood into the useful and potent glycogen of the tissues, and the converse critical situation of the diabetic who is unable to accomplish this adequately.

In some such fashion Krebs has recently visualized the conversion of acetic acid into acetoacetic acid in surviving liver tissue. Acetic acid was condensed with pyruvic acid to provide for the formation of acetoacetic acid. The product formed by a traditional  $\alpha$ -oxidation gave the substance desired as follows:



However, Krebs failed to consider the fact that the acetopyruvic so formed has labile hydrogen on the  $\beta$ -carbon atom, and the following reactions and products could be expected, as well.<sup>6</sup>



Under natural conditions, as in the organism, the pyruvic acid so formed could again condense with acetic acid, and the cycle could be repeated, as long as the pyruvic acid survived or acetic acid was available for the condensation.

Moreover pyruvic acid could condense with acetoacetic acid to form the triketo acid:  $\text{CH}_3\text{COCH}_2\text{COCH}_2\text{COCOOH}$ , which by two successive losses of two carbon atoms would be prepared to repeat the cycle.

The idea that sugar catabolism and fat catabolism could be linked by the formation of an "active" substance by the condensation of acetoacetic acid with some intermediate product of sugar catabolism was perhaps first suggested by Geelmuyden in 1904. The subject has had a long and interesting history, that can not be reviewed here, except to say that the idea and the work done on it, was stimulated by the relation known to exist between the disappearance of ketone bodies and the simultaneous catabolism of some glucose. Of all the suggested intermediate compounds acetopyruvic acid is the only one, prepared and administered so far, that is not objectionable. Animal studies have shown that acetopyruvic acid is not toxic, and that it is quickly metabolized by the intact animal.<sup>7</sup>

One of the perplexing facts of the integration of carbohydrate and fat catabolism, at this level, is that the strict ratio, i.e. one molecule of glucose for two molecules of fat burned, although it is often approached in man, does not seem to be an invariable relation, and is as a matter of fact possibly non-existent in some animals. There is an enormous literature on this subject, but we need only point out

that the considerations developed above provide for any ratio whatever, depending on whether a given molecule of pyruvic acid enters the reaction just once or repeatedly, and on how many inert molecules must be activated by the recapture synthesis.

**General Résume.** The integration of fat and carbohydrate catabolism is not often discussed. Here we have summarized the best information available on both subjects in such a way as to permit of both a separation and an integration of the two catabolisms, under appropriate circumstances, but we have also presented by inference a workable program for future research, by which the validity of the expressed and implied details offered will be determined. This summary and program is constituted of several definite stages or events, that may be visualized as follows:

(a) The fat must be transported from and to the depots. For catabolism it must be mobilized to the tissue site at which the potential energy is to be converted. This is accomplished satisfactorily by conversion of the fat into hydrophilic phospholipids and cholic acid-cholesterol complexes.

(b) The fatty acid must be brought into the oxidizing enzymes of the working cells, and this may be accomplished by the passage of these substances as they are found in the blood into the cells.

(c) In view of all of the known facts it seemed necessary to provide for two distinctly different end-results for the combustion of the fatty acids. Of these  $\alpha$ -oxidation provides for complete or nearly complete combustion to carbon dioxide and water, and the  $\beta$ -oxida-

tion for the combustion with the production of acetoacetic acid.

(d) The normal end-products for these two types of oxidation could be the resistant molecules, acetic and acetoacetic acid, respectively. To provide for their smooth and easy destruction the recapture of these inert substances as active metabolites by a condensation reaction was visualized.

(e) Thus we would have four distinctly different primary mechanisms for oxidation separated from each other in time and space: One involving carbohydrate, two involving fatty acids and finally the recapture synthesis as preliminary to the oxidation of inert intermediate products. These four oxidative mechanisms are viewed as regulated by the mass action effect of the concentration of the acceptor-hydrogen, as reflected by the redox potential, i.e. on a supply and demand basis.

(f) The type of metabolism, whether it is of the normal, fasting or diabetic type, for instance, is determined by the type of metabolites available, and by the functional capacity of the special preparatory mechanisms involved in their ultimate conversion into metabolic hydrogen.

(g) The picture as presented is in some degree crude, and partly so for the sake of simplicity and brevity. It is, however, highly flexible as it should be at this stage. It provides for the overcoming in a controlled way of the innate "reaction resistance" observed with all metabolites, such as glucose and fatty acids, and provides that the chemical events of catabolism shall be controlled, directed and steered into definite channels, which so far as the energy conversion is concerned is achieved through the for-

mation of metabolic hydrogen. The net result and purpose of all the shifting and control is the maintenance of this "fuel" supply at a useful rate compatible with favorable existence.

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<sup>1</sup> This article is supplementary to a longer one published in *Advances in Enzymology*, edited by F. F. Nord and C. H. Werkman, Interscience Publishers, Inc., New York, and in which other details will be found.

<sup>2</sup> Witzemann, E. J., *J. Biol. Chem.*, 95: 219, 247 (1932).

<sup>3</sup> Szent-Györgyi, A. v. "On Oxidation, Fermentation, Vitamins, Health and Disease," Williams and Wilkins Co., Baltimore (1939), p. 60.

<sup>4</sup> Witzemann, E. J., *J. Am. Chem. Soc.*, 48: 202, 208 (1926).

<sup>5</sup> Lehninger, A. L., *J. Biol. Chem.*, 143: 147 (1942).

<sup>6</sup> Lehninger, A. L. and Witzemann, E. J., *J. Am. Chem. Soc.*, 64: 874 (1942).

<sup>7</sup> Lehninger, A. L., Paper in Press.

## CATABOLISM

See Carbohydrate and Fat Catabolism.

## CARBOHYDRATE, FORMATION FROM FAT

The glycerol moiety is converted by the liver to glucose; the conversion of the fatty acids is argued from a low R.Q., e.g. as less than 0.7 in hibernation, or 0.8 to 0.6 in feeding butter to rats, or in plants during germination, or in silkworm metabolism at certain starvation stages.

## CARBOHYDRATE METABOLISM

The higher animals obtain practically all of their energy requirements from the oxidation of carbohydrate and fat. Protein is required for the building of body structures, but it can also be used to furnish energy, by the oxidation of its con-

stituent amino acids, after deamination. The non-nitrogenous molecules apparently are not oxidized as such, but rather as carbohydrates or as fatty acid residues. Accordingly, the amino acids which, after deamination, are capable of yielding glucose or glycogen are known as glucogenic, and those of the fatty acid group as ketogenic. As the culmination of many lines of investigation, Shaffer proposed an elaborate theory of a stoichiometric combination of glucose with the four-carbon ketone bodies resulting from incomplete fat breakdown. This chemical combination was considered essential to the further oxidation of the fat residues. It is now clear that the oxidation of fat is competitive with that of carbohydrate, rather than synergistic. For a few hours after a carbohydrate-rich meal, carbohydrate predominates in the metabolic mixture undergoing oxidation. This suggests some sort of preferential oxidation of this foodstuff, possibly through more successful competition by carbohydrate oxidation enzyme systems for cytochrome. During fasting, or other conditions of carbohydrate deprivation, there is general suppression of carbohydrate oxidation in favor of fat. The liver adjusts to the nutritive situation by decreasing its output of glucose, substituting instead the ketone bodies, which are oxidized readily by most extrahepatic tissues, with the notable exception of nervous tissue, and, possibly, heart and testicle.

In considering the broad field of carbohydrate metabolism, it is convenient to follow ingested carbohydrate through the changes to which it is subjected in being rendered available to and utilized by

the tissues of the body. This involves digestive breakdown of the dietary carbohydrates into glucose and other monosaccharides which are then absorbed and distributed about the body by the blood. The various tissues utilize glucose obtained from the blood either by storing it (principally as glycogen), or by breaking it down. In mammals, at least, the bulk of this latter is by oxidation, although there often is some formation of such intermediates as pyruvic and lactic acids.

The digestion of starches is started by ptyalin, an enzyme present in the saliva, capable of breaking down cooked starch to dextrins and maltose. Since the food ordinarily remains in the mouth only long enough for mastication to take place, most of the effective ptyalin digestion is carried out in the stomach. Fifty per cent of the starch of a mixed meal may be broken down thus, even though ptyalin requires a neutral medium, because of the slow penetration of hydrochloric acid into the bulk of the food mass held in the fundus and body of the stomach prior to active peristalsis in these regions. In the small intestine, the powerful pancreatic amylase produces maltose from starch and from the dextrins resulting from ptyalin action. Maltose is split to two molecules of glucose by maltases present in pancreatic juice and intestinal juice. The disaccharides lactose and sucrose which occur as such in the dietary are split to their constituent sugars by specific enzymes, also found in the intestinal juice.

The carbohydrates are absorbed almost exclusively in the form of the simple sugars produced by appropriate enzyme action. Many

attempts have been made to demonstrate glucose absorption from the stomach; the only clearly successful results have been obtained with the use of a 40% glucose solution, which is so concentrated that it is of little significance in relation to ordinary dietary situations. Absorption of glucose takes place in the jejunum and upper ileum, since the lower ileum shows a very limited absorptive power. No absorbable carbohydrate material normally appears in the caecum. Diffusion—the passage of the dissolved sugar from a concentrated solution to a weaker—might at first thought be considered as the simplest explanation of the absorption of monosaccharides from the intestine, but much evidence exists to support a more complicated actual mechanism. Glucose will pass from the lumen of the small intestine into the blood stream, but not in the opposite direction, even in the presence of the greatly elevated blood sugars of the diabetic person or animal. Glucose will also be absorbed from a solution of a concentration equal to or lower than that in the blood. Glucose, fructose, and galactose, the hexoses commonly encountered as constituent sugars of the dietary carbohydrate, are more rapidly absorbed from the intestine than pentoses, whereas this difference is not shown in absorption from the peritoneal cavity (where the intestinal mucosa is not involved).

The nature of the "active process," presumably involving energy output by the mucosa, is widely accepted as being phosphorylative, although the evidence cannot be considered at all conclusive. The addition of inorganic phosphate to a glucose solution in the intestine will speed up the absorption of the

sugar, and increase the amount of organic phosphate in the intestinal mucosa as well as in the blood serum. The removal of the pituitary or of the thyroid gland decreases glucose absorption, probably through related mechanisms, since thyroxin injection alleviates both deficiencies. No specific information exists as to the detailed nature of this effect. Vigorous attempts have been made to involve the adrenal cortex in the control of a phosphorylative absorption, but more thorough investigations have since revealed that the absorption of everything, including even sodium chloride, is depressed in adrenal cortical deficiency. The use of phlorhizin, which depresses phosphorylations and has yielded such valuable information concerning the phosphorylative nature of glucose reabsorption in the kidney tubules, has given only equivocal information concerning intestinal absorption.

The values obtained for hexose absorption after administration of one sugar alone must be considered as maximal, since a solution of two sugars shows less absorption of each one than when separate tests are made. Furthermore, the presence of amino acids depresses the absorption of a sugar, so that one may consider the absorption of sugars formed during digestion of a mixed meal to be much slower than would be indicated by these experiments.

The simple hexoses absorbed from the small intestine pass via the portal system directly to the liver, where they are removed to a large extent. Glucose is the most important carbohydrate found in blood—it is, in fact, the only free sugar found there in postabsorptive conditions, excepting lactose during

lactation. There are considerable amounts of phosphorylated carbohydrates, especially diphosphoglyceric acid, and the leucocytes have been reported to contain glycogen. The significance of the presence of these last two carbohydrates is not clear, but there can be no doubt about the importance of the blood glucose for the various tissues of the body, especially that of the nervous system. Nerve tissue does not have carbohydrate reserves, and is entirely dependent upon the circulation for amounts of substrate as well as of oxygen adequate to satisfy its energy requirements. Deprivation of oxygen will, of course, be detrimental to any mammalian tissue if sufficiently prolonged, but the central nervous system is the only tissue affected by the lack of glucose, since glucose is the only commonly available one of the few substances which brain oxidizes *in vivo*. If the concentration of blood glucose decreases to about 20 mg. per 100 cc. of blood (as commonly determined and by some considered to be a true sugar value of 0), the animal exhibits hypoglycemic convulsions, leading to coma and death unless sugar is administered. These effects seem to be due primarily to deranged central nervous system function.

Since the liver does not remove all of the extra glucose reaching it in the portal blood after ingestion of a meal containing carbohydrate, a rise in blood sugar level is found. The rise will depend on the amount and type of carbohydrate: starch producing less change than sucrose, because of the requirement of considerably more digestive activity to reach the monosaccharide stage. Determination of the changes in blood sugar values following the



administration of a test dose of glucose is widely used as an assay of the individual's ability to metabolize carbohydrate: the "glucose tolerance test." Normally, the value rises to about 150 mg.% by one hour after one gram of glucose per kilo of body weight, and is back to the resting level by two hours. In the diabetic patient, the starting blood sugar values are often higher than normal, and the rise produced by an equivalent amount of glucose is higher and more prolonged. A similarly lowered glucose tolerance is produced by a high-fat, low-carbohydrate diet for several days prior to the test. The types of glucose tolerance curves obtained in the human under different conditions are illustrated in Figure 1. If the blood

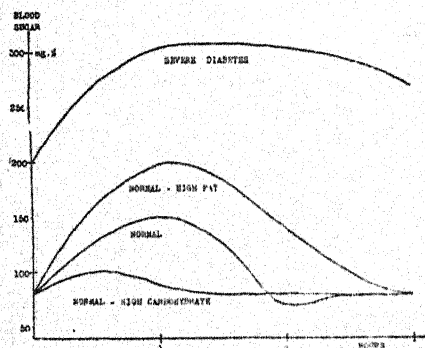


Figure 1. Glucose tolerance curves under different conditions

sugar value rises above about 180 mg.%, tubular reabsorption in the kidney is incomplete, and some sugar will be lost in the urine. Occasionally glycosuria is encountered with blood levels only moderately elevated, as after an ordinary meal. Such a renal glycosuria is apparently due solely to a lower than normal kidney threshold for sugar.

In the normal animal maintained

on an adequate mixed diet, approximately 60% of the glucose which is absorbed and distributed about the body is stored as glucose or as its polymer glycogen, and approximately 40% oxidized within several hours following absorption. Although the liver amounts to only about 4 per cent of the total body weight, it is found to contain 40% of the newly-formed glycogen, the remainder being in the muscles. Since the skeletal muscle accounts for about half of the body's oxygen consumption, it will obviously be the largest consumer of available glucose. The oxidation of carbohydrate by the liver is of distinctly minor quantitative importance, and the retention of such a large amount of the absorbed carbohydrate has an entirely different significance: the liver serves as a storehouse of readily available sugar for the extrahepatic tissues. Glucose is continually leaving the blood as it courses through the extrahepatic tissues, and the venous blood has a lower amount of sugar than the arterial. This withdrawal is met by the addition of glucose formed from liver glycogen. This concept of the functioning of liver to maintain the substrate level of the internal environment was first expressed by Claude Bernard, and further extended by Cannon as part of "homeostasis." It has recently been substantiated by elaborate determinations of the arterial, portal, and hepatic blood sugar levels combined with estimation of the rate of blood flow through the liver. Thus, the post-absorptive addition by the liver of small amounts of glucose to the hepatic venous blood is rapidly changed to a marked retention of glucose when the incoming level rises, as during



the absorption of carbohydrates. As the absorption falls off, so does the hepatic retention, until eventually the liver resumes its original role as the prime source of blood sugar.

The reversible reactions involved between glucose and glycogen, formerly considered due to diastase activity, have recently been shown by the Coris to be due to a series of enzymatic phosphorylations and dephosphorylations:



Glycogenolysis, the breakdown of glycogen, is represented by the reactions from left to right; glycogenesis, the formation of glycogen, from right to left.

Insulin, secreted by the islets of Langerhans in the pancreas, is very important in assisting the liver in its storage function. An increase in the sugar concentration of the arterial blood to the pancreas stimulates the secretion of insulin into the blood, markedly increasing the formation of glycogen from blood glucose removed by muscle and liver. At the same time, the process of glycogenolysis in the liver is inhibited. The blood sugar regulation normally is adequately maintained by the liver, with the help of insulin after carbohydrate ingestion. In the emergency of hypoglycemia, adrenalin secretion by the adrenal medullae is produced, through stimulation of the sympathetic nervous system. This hormone catalyzes glycogenolysis, resulting in an increased addition of glucose to the blood leaving the liver. After removal of the adrenal medullae or destruction of the sympathetic fibers to them, the injection of 2 to 3 units of insulin

per kilo into the animal produces a profound hypoglycemic reaction, although a normal animal receiving the same amount of insulin is not visibly affected. Many instances of hyperactive pancreatic islet tissue have been reported in man, in which cases even the adrenalin mechanism was unable to prevent hypoglycemia several hours after a meal.

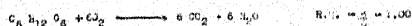
The importance of the liver as a continual source of sugar is demonstrated by the precipitous fall in the blood glucose level following removal of the liver. The extra-hepatic tissues continue their utilization of sugar from the blood, resulting in fatal hypoglycemia in a few hours unless glucose (or one of a very few other carbohydrates) is injected from the outside. Mann and Bollman early determined that about 0.25 gm. of glucose must be injected per kilo per hour to maintain the blood level constant. This value has since been shown to be reduced approximately one-half to one-third by fasting or pancreatectomy prior to the hepatectomy. In these conditions, the glucose which must be added probably represents the requirement of the brain for glucose plus unavoidable loss through lactic acid formation. Figures for hepatic glucose output corresponding closely to the reduced values mentioned above have been obtained by Crandall on unanesthetized fasting dogs, by means of London cannulae.

It has been indicated that normally about 40% of the absorbed carbohydrate is rapidly oxidized. This aspect of the utilization can be measured in the intact animal by carefully controlled measurements of the oxygen consumption and carbon

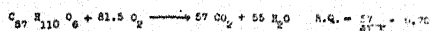
dioxide production, since the proportion:

$\text{CO}_2$  produced/ $\text{O}_2$  used

the "Respiratory Quotient" or "R. Q.") during the oxidation of carbohydrate as the only fuel is 1.00:



and for a typical animal fat 0.70:



The amount of protein undergoing catabolism at the same time is determined from the urinary nitrogen excretion, since most, if not all, of this has been derived from protein. Samples of the liver and muscle of the animal for carbohydrate analyses are also of great value when one can be sure that they are representative. Rarely is it possible or practical to obtain every bit of information one might consider desirable in each experiment, so that concepts must be assembled from many different experiments.

By means of respiratory studies combined with the determination of blood and other tissue carbohydrate changes, a reasonably complete overall picture of the glucose utilization is being assembled. The statements made earlier in this discussion were based on such information obtained on normal well-fed animals in the post-absorptive state (12 to 18 hours after the previous feeding), the standard condition. The state of nutrition and the endocrine balance of the animal have been found to be two predominant factors governing the utilization of carbohydrate, with the probability that the nutritional effect is produced principally through the en-

docrines. Because of this, we shall consider the endocrine effects before going into detail as to the nutritional.

The thyroid gland regulates the metabolic activity of all cells in the body, hence it affects carbohydrate metabolism along with fat and protein. Hyperthyroidism producing a generally increased rate of oxygen consumption, causes a lowered glucose tolerance together with reduced glycogen stores. A high-fat diet produces similar changes in carbohydrate metabolism, and the hyperthyroidism effects are probably due mostly to a reduction in amount of carbohydrate available to the animal caused by the increased rate of oxidation rather than a specific thyroid effect.

Insulin is of prime importance in the storage and oxidation of glucose, especially in the skeletal muscles. The injection of insulin in reasonable amounts, together with glucose, causes a rapid transfer of the sugar from the blood stream into liver and muscle, where it is partly deposited as glycogen and partly oxidized. If the insulin be given alone, it will cause a prompt fall in blood sugar level, finally resulting in convulsions if the dose was large enough. Before actual convulsions appear, the lowered blood glucose has produced sympathetic stimulation of adrenalin secretion. This hormone favors glycogenolysis, the opposite of the insulin effect, thus tending to return sugar to the blood stream. As has been stated, the normal maintenance of a steady glucose concentration in the blood probably involves the liver principally, with the insulin mechanism being stimulated by the ingestion of carbohydrate. Adrenalin is reserved for emergen-

cies such as hypoglycemia, fear, rage, and other conditions in which a rise in blood sugar is advantageous. Although the glucose removed by muscle tissue from the blood is changed into glycogen, adrenalin and other glycogenolytic agents cause the production in this tissue of lactic acid, not glucose. Therefore, the muscle is incapable of maintaining the blood sugar level, a function which belongs exclusively to liver, as we have seen. The Coris and Himwich, independently discovering that liver could remove from the blood the lactic acid produced by muscle, proposed a muscle-liver "lactic acid cycle," with the liver replenishing the blood sugar with glucose formed from muscle lactic acid. More recently, the hepatic part of this cycle has been found to operate only when the animal is fasting or shows high blood lactic acid levels. Therefore, muscle (probably including cardiac) must itself remove and reconvert the small amounts of blood lactic acid produced during mild exercise, but is aided in such carbohydrate conservation by the liver in severe exercise, asphyxia, etc.

Pancreatectomy, by removing the source of insulin, results in experimental diabetes: the blood sugar rises, due to inadequate glycogen storage and retention, to hyperglycemic levels of 250 to 500 mg.%. This produces a marked glycosuria. There is a decreased oxidation of carbohydrate, thereby shifting the energy requirement over onto fat. The liver, as well as other tissues, is involved, since the hepatic output of glucose is replaced by the ketone bodies from partial oxidation of fat, only enough glucose being added to the blood to satisfy the

central nervous system, and to replace that lost in the urine.

The cortex of the adrenal gland secretes substances which affect three types of body functions—sex physiology, electrolyte metabolism, and carbohydrate metabolism. As yet no substantial theory has been offered to correlate even the two metabolic functions. Cortin, the active extract of the adrenal cortex, depresses carbohydrate oxidation, and at the same time stimulates gluconeogenesis from protein. Removal of the cortical tissue of the depancreatized animal lessens the severity of the diabetic condition. The effects are quite comparable to those following pituitary removal in the depancreatized animal, and will be discussed more fully shortly.

In the past decade, with the growing realization of the functioning of the endocrine organs as a well-integrated system instead of an uncoordinated series of structures, the anterior pituitary has emerged as the coordinator of the system, through its "trophic" principles. In fact, it becomes very difficult to be absolutely certain in many instances that an alleged pituitary effect is not actually exerted indirectly through some other endocrine gland. The pituitary is able to stimulate as well as inhibit the secretion of insulin by the pancreas. Houssay showed that a series of injections of anterior pituitary extracts produced a temporary hyperglycemia and glycosuria, and lowered carbohydrate tolerance. Young and, later, other workers, were able to produce permanent diabetes by the protracted injection of large amounts of anterior pituitary extracts. Analysis of the insulin content of the pancreases of such animals showed a nearly complete

absence of insulin, suggesting that the gland had been exhausted after too intensive a stimulation with pancreatropic factor.

The anterior pituitary aids in maintaining the carbohydrate levels of the body: in the hypophysectomized animal, there is an excessive proportion of administered carbohydrate oxidized immediately with less being stored, and the animal is also unable to maintain its blood sugar at the expense of body protein. Because of these two defects, there is a striking sensitivity to procedures tending to produce hypoglycemia, such as fasting or insulin injection. The injection of 0.75 unit per kilo of insulin into a normal dog will produce only an analytically detectable lowering of blood sugar, while that amount in a hypophysectomized dog will often cause a dangerous hypoglycemic reaction. This insulin sensitivity has often been attributed to the removal of a "glycotropic" factor normally secreted by the pituitary, but the effect again probably is an indirect one. The adrenalin mechanism, discussed previously in connection with the maintenance of the blood sugar, is definitely deficient after hypophysectomy: it is not yet clear whether this is due to a diminished secretion or to a diminished effectiveness of adrenalin. The interesting possibility of a potentiation of adrenalin action by desoxycorticosterone, one of the adrenal cortical hormones, would fit in well as explaining part of the absence of adrenalin effect on a decreased effectiveness basis. In addition, the lowered glycogen stores present less opportunity for glycogenolysis.

The removal of the pituitary from depancreatized animals produces a

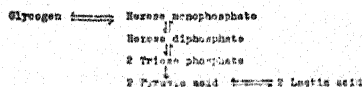
striking amelioration of the diabetes. The marked hyperglycemia is reduced to normal values, but shows abnormally wide fluctuations between the peaks during carbohydrate absorption and the depressions during fasting. The rate of gluconeogenesis from protein is decreased, and increased amounts of carbohydrate are deposited and oxidized. A similar effect occurs after removal of adrenal cortical tissue. One is immediately struck by the possibility that the effect of hypophysectomy is produced through decreased cortical function, that is, that normally the pituitary exerts its "anti-insulin" effects by stimulating the secretion of cortical hormones.

The incomplete but definite return toward normal carbohydrate metabolism produced in the depancreatized animal by removal of the pituitary or adrenal cortices suggests the double nature of the hormonal regulation. Insulin increases carbohydrate utilization through regulated storage and oxidation; the anterior pituitary (partly, at least, through the adrenal cortical tissue) decreases carbohydrate utilization and increases gluconeogenesis. These two opposing controls allow a wide range of adjustments on the part of the animal to different nutritional conditions. One extreme situation, represented by the ingestion of large amounts of carbohydrate which must be taken care of at once for the future use of the body, stimulates the secretion of insulin, which catalyzes utilization reactions. To insure that the stored carbohydrate will be rapidly available as glucose in an emergency, the sympathetic nervous system-adrenalin mechanism exists. At the opposite extreme, during fasting, in

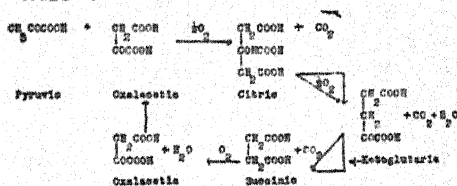
which condition there is complete lack of carbohydrate intake, the body stores of this foodstuff, laid down when intake was high, must be carefully used. Through the adrenal cortical hormone, carbohydrate oxidation by extraneural tissues is suppressed, and protein catabolism increased to make available more glucogenic amino acids. The glucose formed from these replaces the blood sugar removed and oxidized by the nervous system.

The hepatic production of ketone bodies, which process increases as the hepatic glucose production falls, has not been shown conclusively to be under hormonal control, although, as easily oxidizable substrates, the ketone bodies apparently are substituted for the glucose. Anselmino and Hoffman ten years ago showed that injection of anterior pituitary extracts would increase the ketone body content of the blood, but subsequent work has not established whether this should be considered a specific hormonal effect on the liver, or an indirect effect resulting from suppression of carbohydrate oxidation. Carbohydrate seems to be preferentially oxidized by all tissues, but in the absence of carbohydrate oxidation, whether due to lack of that foodstuff or to hormonal inhibition, the tissue fatty acid oxidation enzymes come into action to satisfy the ever-present energy requirement. The fundamental nature of these two opposing reactions is suggested by the fact that they will proceed in the absence of both controlling hormonal factors, as in the hypophysectomized-depancreatized animal. It is obvious, however, that the controls are of tremendous importance in rendering the reactions adaptable to extremes of nutritional conditions.

The detailed nature of the insulin effect still is not clear. Despite the many suggestions that insulin is part of a carbohydrate oxidation enzyme system, most of the concrete evidence thus far obtained points to insulin as speeding some preliminary step in the process, possibly a phosphorylation, which increases the accessibility of the glucose to intracellular enzymes. In fact, the details of the oxidative process itself are not clear, although many possibilities have been presented. The greatest amount of evidence concerns anaerobic reactions, which have been worked into a series starting with glycogen, and finally resulting in the production of lactic acid:



According to one concept, in the presence of oxygen the lactic acid is either oxidized or not formed, pyruvic acid being the form oxidized. Krebs has proposed a cyclic series of events, the "citric acid cycle," into which pyruvic acid is first incorporated, then gradually broken down, yielding  $\text{CO}_2$  stepwise\*:



Although not specifically stated, the series of anaerobic reactions is brought in by implication in the production of the pyruvic acid required for the citric acid cycle. In normal man, the administration of glucose causes an increase in the blood pyruvic acid level, a response which is absent in the human



diabetic. This suggests that pyruvic acid is of importance in the normal utilization of carbohydrate. As in thiamin deficiency, however, the total rise in blood pyruvate is quantitatively insignificant in relation to the amount of carbohydrate fed. For this reason, the finding is at present only suggestive.

Engelhardt and Barkash placed the split between anaerobic and aerobic processes earlier than pyruvic acid, at the hexose monophosphate stage: in the presence of oxygen the anaerobic series is circumvented by oxidation on the non-phosphorylated end carbon of the hexose to produce a phosphohexonic acid. Stepwise oxidation of the carbon chain then continues from the carboxyl carbon. Still another proposal is that there is no relation between the events in the absence and in the presence of oxygen, beyond the starting substances, glycogen and glucose.

Because the contracting muscle oxidizes large amounts of carbohydrate, this preparation has been widely used in the study of carbohydrate breakdown. However, the picture here is complicated by the apparently necessary involvement of the glycogen-lactic acid transformation and resynthesis, independent of the foodstuff whose oxidation finally supplies the necessary energy for the contractile process. The best evidence available indicates that the breakdown of adenylyl pyrophosphate is the closest to the actual contraction, and that phosphocreatin is able to cause restitution of the adenylyl pyrophosphate. The breakdown of glycogen to lactic acid can accomplish the resynthesis of the phosphocreatin, but whether it does so under conditions of adequate oxygen supply is today

being seriously questioned. Even should this be the case, the work of Shorr shows clearly that the resynthesis of the glycogen can be accomplished at the expense of the oxidation of fat as well as carbohydrate.

Since a large proportion of carbohydrate ingested above the caloric needs of the animal is deposited as fat, this aspect of carbohydrate utilization is also important. Although several plausible theoretical formulations have been advanced to account for the transformation, little is known of the intermediate steps. Considerable work has been done showing that the fatty acids in the fat deposited by animals on a carbohydrate-rich diet are highly saturated, suggesting the formation of palmitic and stearic acids. McHenry has obtained evidence showing a requirement for thiamin at some stage of the transformation. This would suggest that the six-carbon chain is at least broken in two before transformation. The reactions are probably very complicated, since a marked decrease in the state of oxidation of the molecule is produced in the change from carbohydrate ( $O:C=1$ ,  $O:H=0.5$ ) to fatty acid ( $O:C=0.11$ ,  $O:H=0.06$ ). This would involve a considerable transfer of H from some donor, as well as the formation of large amounts of water.

Carbohydrate exhibits to a much more marked extent than fat the ability to reduce the amount of endogenous protein undergoing catabolism during fasting or during a very low protein regime—"protein sparing." This effect is due predominantly to the direct removal of the stimulus for gluconeogenesis, since the ingestion of glucose will immediately result in hypergly-



cemia. In addition, carbohydrate residues, such as pyruvic acid, may be transformed into amino acids, and replace amino acids lost from body protein.

Throughout this discussion, the point of view of the so-called "Under-utilization" school has been presented, since it appears to the present author that the bulk of the evidence supports this view. It should be pointed out that there is an opposing school, that of "Overproduction" (cf. Soskin<sup>11</sup>). The views of this group are based on the conviction that fatty acids are transformed into carbohydrate in the liver, a process for which there are many philosophical arguments, but no concrete evidence. This group holds that the depancreatized dog oxidizes as much glucose at its elevated blood sugar level as the normal at the lower level, and that the principal function of insulin is to regulate the production of glucose from fatty acids in the liver. Stadie has shown that isolated liver tissue, studied in the Warburg apparatus, forms ketone bodies from most of the fatty acids broken down, and that there is insufficient O<sub>2</sub> consumed by the tissue to transform a significant amount of fatty acid into carbohydrate, after deducting the oxygen required for known metabolic processes. Crandall and co-workers have recently obtained clear evidence that the liver in vivo does not increase its glucose output in diabetes. The glucose which it does add to the blood can be calculated as arising from lactic acid and protein and supplying the central nervous tissue with its needed substrate. In order to compensate for the lack of glucose supply for the other tissues, the liver adds the

readily oxidizable ketone bodies, formed from fatty acids. Thus the overproduction thesis is not supported, and a definitely diminished glucose utilization is shown.

See Creatine and Creatinine Metabolism, Carbohydrate and Fat Catabolism.

\*The reactions apparently involved in the cycle are only partially noted here in order to emphasize the principal thesis. Those interested in greater detail are referred to Evans.<sup>6</sup>

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#### REVIEW REFERENCES

- <sup>1</sup> Bollman, J. L., and Mann, F. C. The physiology of the impaired liver. *Ergeb. der Physiol.*, 38: 445-492 (1936).
- <sup>2</sup> Burk, D. A colloquial consideration of the Pasteur and neo-Pasteur effects. *Cold Spring Harbor Symp. on Quant. Biol.*, 7: 420-459 (1939).
- <sup>3</sup> Chambers, W. H. Undernutrition and carbohydrate metabolism. *Physiol. Rev.*, 18: 248-296 (1938).
- <sup>4</sup> Cori, C. F. Phosphorylation of carbohydrates. *Symp. on Resp. Enzymes*, pp. 175-189, 1942, Univ. of Wisconsin Press, Madison, Wisconsin.
- <sup>5</sup> Drury, D. R. Control of blood sugar. *J. Clin. Endocrin.*, 2: 421-430 (1942).
- <sup>6</sup> Evans, E. A., Jr. Pyruvate oxidation and the citric acid cycle. *Johns Hopkins Hosp. Bull.*, 69: 225-239 (1941).
- <sup>7</sup> Haist, H. E., Campbell, J., and Best, C. H. The prevention of diabetes. *N. E. J. of Med.*, 223: 607-615 (1940).
- <sup>8</sup> Houssay, B. A. The hypophysis and metabolism. *N. E. J. of Med.*, 214: 961-971 (1936); Carbohydrate metabolism. *ibidem*, 214: 971-986 (1936).
- <sup>9</sup> Long, C. N. H., Katzin, B., and Fry, E. G. The adrenal cortex and carbohydrate metabolism. *Endocrin.*, 26: 309-344 (1940).
- <sup>10</sup> Shorr, E. The relation of hormones to carbohydrate metabolism in vitro. *Cold Spring Harbor Symp. on Quant. Biol.*, 7: 323-348 (1939).
- <sup>11</sup> Soskin, S. The blood sugar: its origin, regulation, and utilization. *Physiol. Rev.*, 21: 140-193 (1941).

<sup>12</sup> Stadie, W. C. Fat metabolism in diabetes mellitus. *J. Clin. Inves.*, 19: 843-861 (1940).

<sup>13</sup> Young, F. G. The pituitary gland and carbohydrate metabolism. *Endocrin.*, 26: 345-351 (1940).

See also Digestion.

## CARBOHYDRATES

A group of polyhydroxy alcohols, usually in multiples of straight 5 and 6 carbon chains, which are used as a source of energy and for structure in plants and animals. Formed of C, H and O in the proportions of one molecule of H<sub>2</sub>O to every carbon.

## CARBOHYDRATES AND MENTAL STATES

See Psychiatry, Biochemistry of.

## CARBOHYDRATES. CLASSIFICATION OF

Various schemes of classification have been proposed. One of the most convenient is:

### I. Simple Sugars (Monosaccharides)

Monoses, dioses, trioses, tetroses, pentoses, hexoses, heptoses, octoses, nonoses and decoses (formaldehyde is usually ruled out.)

### II. Compound Sugars

Disaccharides (dipentose, pentose-hexose, methyl pentose-hexose, dihexose); trisaccharides, tetrasaccharides, polysaccharides (pentosans, methyl pentosans, hexosans, condensed amino saccharides, mixed pentosans, mixed hexosans).

### III. The Cycloses or Cyclitols

Inositols, quercitols, tetritols.

For details see individual entries.

## CARBOHYDRATE SYNTHESIS

See Photosynthesis.

## CARBOHYDRATE TOLERANCE

The capacity of the body to assimilate carbohydrates, as determined by the blood sugar concentration; reduced in liver poisoning and diabetes.

## CARBONIC ANHYDRASE

The enzyme which catalyzes the splitting of CO<sub>2</sub> from carbonic acid. It is a zinc protein.

## CARBONIFEROUS ERA

See Paleozoic.

## CARBON MONOXIDE HEMOGLOBIN TEST

See Michel Reagent.

## CARBON MONOXIDE POISONING

See Psychiatry, Biochemistry of.

## CARBONYLDIAMIDE

See Urea.

## CARBOXYHEMOGLOBIN

Compound of hemoglobin with carbon monoxide, incapable of reacting with oxygen and dissociating with greater difficulty than the analogous oxygen compound.

## CARBOXYLASE

A thiaminoprotein enzyme of yeast which in the presence of Mg or Mn promotes the decarboxylation of pyruvic acid and other alphaketomono-carboxylic acids.

## CARBOXYL-PHOSPHATES

See Phosphate Bond Energy.

## CARBOXYMETHYL-S-CYSTEINE

HOOC-CH<sub>2</sub>-S-CH<sub>2</sub>-CH(NH<sub>2</sub>)-COOH; is excreted as a mixed disulfide.

## CARBOXYPEPTIDASE

A group of polypeptide hydrolyzing enzymes that split off the end of a polypeptide chain, the

amino acid that has a free carboxyl group.

## CARBOXYPOLYPEPTIDASE

See Autolysis.

## CARBROMAL

Alpha-ethylbutyryl-carbamide, a sedative and hypnotic; uradal; adalin.

## CARCINOGENESIS BY NITROGEN-CONTAINING COMPOUNDS

In 1932, Yoshida showed that feeding the azo compound, 4'-amino 1-3-azotoluene caused liver cell tumors in rats. Sasaki, in 1935, confirmed this work. In 1937, Kinoshita showed that butter yellow, p-dimethylaminoazobenzene, produced hepatomas and cholangiomas in rats fed this compound. Generally, rice was the staple diet.

Various other nitrogen containing compounds have been investigated and found to have carcinogenic activity. Among the very many studied, a few are 1,2-benzacridine and several of its mono and dimethyl derivatives, several benzophenothiazines and dibenzophenothiazines, dibenzcarbazoles and azonaphthalenes. For a complete list of chemicals studied for carcinogenic activity, see the publication of the National Cancer Institute, "Studies of Compounds Showing Carcinogenic Activity."

Among the most thoroughly studied of the nitrogen containing carcinogens are butter yellow and aminoazotoluene. A few details about these are presented, largely as abstracts of the papers referred to.

### I. Action of Butter Yellow in Rats<sup>1</sup>

A standard method of administration of B.Y. is as a 3% solution in olive oil. 20 cc. of

this solution are mixed with 1000 gms. of the basal diet, frequently unpolished Texas rice, and this is fed ad libitum. Usually a small piece of carrot is given for vitamin A. At the end of thirty days of feeding there is little change in gross appearance. At the end of two months, the capsule is somewhat irregular, with some nodule formation and slight evidences of malignancy. Histologically there is proliferation of fibrous connective tissue, showing annular cirrhosis. After three months there are well defined grayish or yellowish white nodules, with evidence of extensive malignant changes. After 5 months of feeding, practically all the livers showed extensive cancer growths. There were large massive nodules, some white and soft, others hemorrhagic. Some of the livers weighed up to 75 grams, as compared with the normal of 8 grams, with 90% of the organ being cancerous.

### II. Effect of Feeding Carcinogens on Liver Function and Content

a)<sup>2</sup> Livers of rats fed amino-azo toluene until hepatomas appeared had less vitamin A than normal, and the tumors were devoid of it. Butter Yellow had no effect on hepatic vitamin A. Several other compounds had an effect, but there was no correlation between carcinogenic strength and vitamin A contents.

b)<sup>3</sup> Rats fed butter yellow show conjugated p-amino phenol in the urine, probably with glucuronic acid. Liver slices from rats fed butter yellow conjugate

more dl- borneol with glucuronic acid than do slices from normal rats. This is true even when the experimental livers have hepatomas or cholangiomas. Animals fed butter yellow excreted more glucuronides in the first one hundred days than normal rats, but after that they secreted a good deal less. This latter effect may be due, at least partly, to a liver food intake.

c)<sup>4</sup> Cohen studied the transaminase activity of homogenized liver of butter yellow fed rats in the system:  $1+ -$  glutamic acid and oxaloacetic acid  $\leftrightarrow$   $\alpha$ -ketoglutaric acid and aspartic acid. After fifty days of feeding, the livers tended to show progressively diminishing transaminase activity. Nakatani showed that there is a progressive increase in anaerobic glycolysis with continued butter yellow feeding. Aerobic glycolysis showed normal levels up to the time of tumor formation, then went high.

Greenstein showed that there was decreased enzyme activity in animals fed butter yellow in the following systems; catalase, arginase, xanthine dehydrogenase.

d)<sup>5</sup> Kensler, Suguira, and Rhoads studied the  $Q_{O_2}$ , coenzyme I and riboflavin content of livers of rats fed four different diets: 1. Normal diet, 2. Basal diet, 3. Basal diet and butter yellow, 4. Basal diet and butter yellow and 15% dried brewer's yeast. The  $Q_{O_2}$ 's do not change. The riboflavin and coenzyme I of the rats fed the basal diet, and the basal diet plus butter yellow are low, the latter being the lower of the

two. The addition of the yeast restores these levels to normal. Butter yellow tumor tissue has very low values. The coenzyme I of the kidneys is not effected.

### III. Metabolism of Butter Yellow in Rats<sup>6</sup>

By ether extraction of unhydrolyzed and hydrolyzed urine, and separation of the two ether extracts into phenolic, neutral, basic, and phenolic-basic fractions; and purification of the various fractions by high vacuum distillation and chromatographic absorption, Stevenson, Dobriner, and Rhoads were able to isolate aniline, p-amino phenol, n-acetyl p-amino phenol, N,N'- dimethyl p-phenylenediamine ; p-phenylenediamine; N,N'-diacetyl p-phenylenediamine. They outline the following as the course of the metabolism of butter yellow: 2 main routes; (1) through p-aminophenol to N-acetyl-p-aminophenol and (2) through p-phenylenediamine to N, N'-diacetyl-p-phenylenediamine.

### IV. The Fact of Metabolites of Butter Yellow<sup>7</sup>

It was mentioned in a previous section, (II-d) that livers fed butter yellow are low in diphosphopyridine nucleotide (coenzyme I) activity. Kensler, Dexter, and Rhoads<sup>7</sup> studied the effect of butter yellow and its metabolites on fermentation in a yeast apozymase system, where the D.P.N. is the limiting factor, to see what compound or compounds was responsible for this effect. Butter yellow caused no inhibition, p-aminophenol showed only slight

inhibition, but p-phenylenediamine, and its N,N, dimethyl derivative showed strong inhibition. Various other compounds similar to p-phenylenediamine showed marked inhibition, in the degree of inhibition being approximately parallel to the stability of the free radical obtained by oxidation of the compound. The acetyl derivatives of the compounds are not toxic, and their free radicals are not stable. Acetylation is therefore a mechanism of detoxification of the butter yellow metabolites. The inhibition is due to a competition between the compound and the D.P.N. for an enzyme active in fermentation, possibly triosephosphate dehydrogenase. When more D.P.N. is added, inhibition is diminished. The fact that alloxan and iodoacetic acid, which react with sulfhydryl groups, also inhibit the D.P.N. system suggests that inhibition is due to inactivation of SH groups by the metabolites.

b)<sup>8</sup> Kensler, Young, and Rhoads showed that p-phenylenediamine and its N-methylated derivatives strongly inhibit the activity of a yeast carboxylase system. The authors indicate that the inhibition is due to the inactivation of the catalytically active protein enzyme, partly on the following grounds.

Cohen<sup>4</sup> (See II-C) found that the order of inhibition of liver transaminase activity by possible butter yellow metabolites is Quinone > N-Methyl-p-phenylenediamine > N,N-dimethyl-phenylenediamine > p-pheny-

lenediamine. Kensler found that the order in the D.P.N. system is N,N-dimethyl p-phenylenediamine > p-phenylenediamine, > quinone. He ascribes inhibition in the D.P.N. system to inactivation of SH groups. The difference in order of activity plus the fact that transaminase is not inhibited by alloxan or iodoacetic acid, indicates that there is a difference in the mechanism of the inhibition in the two systems.

## V. Effect of Diet

### 1. Rice Bran Extract<sup>1</sup>

Rats fed butter yellow were given an adjunct of a small amount of ethereal extract of rice bran. After 150 days of feeding, 90% of the controls had liver cancer; 68% of the treated animals had normal livers, and 32% had a slight granular appearance. However, the effect seemed to be inhibitory rather protective, for after 153-250 days, 61% of the treated animals showed either cancer or the typical cirrhosis that proceeds it.

### 2. Yeast Extract<sup>1</sup>

An ethereal extract of yeast was added to the butter yellow diet. After feeding 100-223 days, 100% of the controls had cancer, 36% of the treated animals were normal, 14% showed cirrhosis, 50% had cancer.

### 3. 15% Whole Yeast<sup>1</sup>

Whole yeast was added to the butter yellow diet. After feeding for 104-284 days, 100% of the controls had cancer, while only 2 out of 34 treated rats showed cirrhosis, with all the others being normal. 6% and 3% yeast had progressively less effect.

#### 4. Casein<sup>1</sup>

The addition of casein to the butter yellow diet had no appreciable effect on cancer production though the animals had a healthier appearance. The same is true of adding carrot to the diet.

The protection afforded by the above compounds was in direct relation to the amount of riboflavin they contained. However, feeding up to 5 mgs. of pure riboflavin per day per rat gave very little protection. Nicotinic acid or casein alone gave no protection. Nicotinic acid plus riboflavin gave a 50% decrease in the amount of cancer resulting. When the basal diet was supplanted with riboflavin and casein, only 1 rat out of 16 showed cancer after 150 days, while 4 showed histological changes. 97% of the untreated animals had cancer.<sup>9</sup>

Because of the above work, Du Vigneaud and others tried a number of other B complex vitamins, as well as ergosterol and vitamin K. These did not significantly improve the protection afforded by riboflavin plus casein. It was found that biotin, at a level of 28 per day destroys the protection afforded by riboflavin plus casein.<sup>10</sup>

HILTON LEVY.

#### BIBLIOGRAPHY

<sup>1</sup> Sugira & E. Rhoads, "Experimental Liver Cancer in Rats, and its Inhibition by Rice Bran Extract, Yeast and Yeast Extract." *Cancer Research*, Vol. I, p. 3, 1941.

<sup>2</sup> Baumann, Foster & Lauik, "Effect of Certain Carcinogens on Vitamin A in the Liver." *J. Nutrition*, 21: 431, 1941.

<sup>3</sup> Kensler, Young & Rhoads, "Glucuronic Acid Production in Vitro Liver

Slices from Rats Fed Dimethylaminoazobenzene." *Proc. Soc. Exptl. Biol. Med.*, 48: 22-24, 1941.

<sup>4</sup> Cohen, Hekhuis & Sober, "Transamination in Liver Rats Fed Butter Yellow." *Cancer Research*, 2: 405, 1942.

<sup>5</sup> Kensler, Sugira & Rhoads, "Coenzyme I and Riboflavin Content of Livers of Rats Fed Butter Yellow." *Science*, Vol. 91, p. 623, 1940.

<sup>6</sup> Stevenson, Dobriner & Rhoads, "Metabolism of Butter Yellow in Rats." *Cancer Research*, 2: 160, 1942.

<sup>7</sup> Kensler, Dexter & Rhoads, "Inhibition of a Diphosphopyridine Nucleotide System by Split Products of Butter Yellow." *Cancer Research*, 2: 1, 1942.

<sup>8</sup> Kensler, Young & Rhoads, "Inhibition of Yeast Carboxylase by Split Products of N,N-Dimethylaminobenzene.

<sup>9</sup> Kensler, Sugira, Young, Halter & Rhoads, "Partial Protection of Rats by Riboflavin with Casein against Liver Cancer Caused by Dimethylaminobenzene." *Science*, 93: 308, 1941.

<sup>10</sup> Du Vigneaud et al, "Procarcinogenic Effect of Biotin in Butter Yellow Tumor Formation." *Science*, 95: 174, 1942.

#### CARCINOGENETIC HYDROCARBONS

The active constituents in coal tar causing certain skin cancers are 1,2-benzpyrene and 1,2-benzanthracene. Derivatives are more active, especially methylcholanthrene, which is 5,6-dialkyl-1,2-benzanthracene. A relationship to bile acids, sex hormones and sterols in general is suggested.

Reference: Fieser, L. F., *The Chemistry of Natural Products Related to Phenanthrene*.

#### CARDAMOM

Dried seeds of *Elataria cardamomum*, whose tincture is used as a stimulant and flavor.

#### CARDIA

See Gastro-Enterology.

#### CARDIAC GLYCOSIDES

See Steroids, *Digitalis Glycosides*.



**CARDIAZOL**

See Metrazol.

**CARDIAZOL TEST**

See Zwikker.

**CARDIOVASCULAR DRUGS**

See Pharmacology.

**CARIES**

See Teeth, Biochemistry of.

**CARMINIC ACID**

The coloring compound of cochineal.

**CARNAUBANOL**

$\text{CH}_3(\text{CH}_2)_{22}\text{CH}_2\text{OH}$ ; a saturated fatty alcohol found in carnauba wax and lanolin.

**CARNAUBIC ACID**

A saturated fatty acid,  $\text{CH}_3(\text{CH}_2)_{22}\text{COOH}$ , found in carnauba wax.

**CARNITINE**

Alpha-hydroxy-gamma-butyro-betaïne, a constituent of muscle.

**CARNIVORA**

Order of flesh eating animals.

**CARNOSINE**

$\beta$ -alanylhistidine.

A dipeptide found in the skeletal muscles of reptiles and vertebrates.

**CAROPHYLLENES**

Isomeric sesquiterpenes,  $\text{C}_{15}\text{H}_{24}$ , of clove oil.

**CAROTENE**

Carotin; commonly described as existing in 3 forms,  $\alpha$ ,  $\beta$ , and  $\gamma$ . Their formulas have been worked out relative to vitamin A so that the  $\beta$  form yields two molecules of the vitamin, while the others can furnish only one. For this reason the  $\beta$  form is often described as  $\beta$ ,  $\beta'$ -carotene. All the carotenes have the formula  $\text{C}_{40}\text{H}_{56}$ . Many other isomers are being isolated by chromatographic analysis. Both plants

and animal products contain them, e.g., carrots, alfalfa, liver, butter. An alcohol, cryptoxanthine,  $\text{C}_{40}\text{H}_{58}\text{OH}$ , is closely related to  $\gamma$ -carotene, and also yields one molecule of vitamin A,  $\text{C}_{20}\text{H}_{29}\text{OH}$ , on oxidative fission. In the carotenoids various ring residues have been identified so that  $\alpha$ -carotene has been re-named structurally as  $\beta$ - $\alpha'$ -carotene, and  $\gamma$ -carotene as  $\beta$ -lyco- $\beta'$ -carotene. There is also a  $\delta$ -carotene which turns out to be  $\beta$ -lyco- $\alpha'$ -carotene with no provitamin value, which is due only to the beta ionone residue.

**CAROTENE OXIDASE**

An enzyme of various beans which promotes the oxidation of carotene, xanthophyll, various vegetable oils, probably by the addition of oxygen at a double bond.

**CAROTENE TEST**

See Levine-Bien.

**CAROTENOIDS**

Carotenoids are hydroaromatic or aliphatic fat soluble  $\text{C}_x\text{H}_y$  or  $\text{C}_x\text{H}_y\text{O}$  compounds, which can be formulated as condensation products of eight isoprene groups. They contain seven to eleven conjugated double bonds, causing characteristic absorption bands, accounting for the yellow, orange or red color of all carotenoids. The chain, with a methyl group on every fourth carbon, may terminate at one or both ends in a tri-methyl cyclohexene ring. The carotenes comprise hydrocarbons, secondary alcohols, ketones and acids. They occur in the free state, as esters, as glycosides, and as "symplexes" with proteins (e.g. rhodopsin, visual purple; astacene, in crustacean pigments, etc.). Carotene itself ( $\text{C}_{40}\text{H}_{56}$ ) and xanthophyll ( $\text{C}_{40}\text{H}_{56}\text{O}_2$ ) accompany chlorophyll in all green plants. Other specific

carotenoid pigments occur in algae and in special organs of higher plants (root of *Daucus carota*, fruit of maize, red pepper, tomato, etc.). Some lower animals contain special carotenoids while the carotenoid in the normal and pathological (xanthomatous) deposits, corpus luteum and egg yolk in vertebrates are of alimentary origin. Axerophthol, a colorless split product of certain carotenoids, is Vitamin A, and crocetin and safranin act as "external hormones" in the sex cycle of certain algae; otherwise the biological significance of the carotenoids is still obscure.

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References:

See Chapter 14, by Marston T. Bogert, in H. Gilman's *Organic Chemistry*, New York, 1938, and monographs, by E. Lederer, *Les Carotenoides des Plantes*, Paris, 1934, and *Les Carotenoides des Animaux*, Paris, 1935.

CAROTENOIDS AND GENES

See Genetics, Biochemical.

CAROTENOIDS, SPECIFIC

Light yellow to deep-red plant and animal pigments, extractable by fat solvents and having a structure resembling carotene, namely a carbocyclic or semi-carbocyclic configuration attached to an unsaturated polyene hydrocarbon chain. A relationship to phytol is indicated. The polyene hydrocarbon chain is  $C_{22}H_{28}$  and is common to the group. Besides the carotenes (q.v.) the following are of importance: Lycopene, found in tomato, watermelon, etc., is  $\beta$ - $\beta$ -lycopen; xanthophyll or lutein, found in green leaves, flowers, corpus luteum, etc., is 3-3'-dihydroxy- $\beta$ - $\alpha'$ -carotene; rhodoxanthin, from the of the yellow *Zea mays* is 3-3'-fruit of the yew, is 3-3'-diketo-4-4'-dehydro- $\beta$ - $\beta'$ -carotene; zeaxanthin

dihydroxy- $\beta$ - $\beta'$ -carotene; fucoxanthin of the brown algae, *Fucus* sp., is  $\alpha$ - $\alpha'$ -fucoxanthin; cryptoxanthin from papaya and maize is 3-hydroxy- $\beta$ -carotene- $\beta'$ -carotene; capsanthin from the ripe fruit of *Capsicum annum* is 3-hydroxy- $\beta$ -carotene-5'-desoxy- $\alpha'$ -fucoxanthin; helenien from the flowers of the *Helenium* sp., is  $\beta$ - $\alpha'$ -carotene-3-3'-dioldipalmitate; physalien from asparagus is  $\beta$ - $\beta'$ -carotene-3-3'-dioldipalmitate; astacene from various crustacea is 3-3'-4-4'-tetraketo- $\beta$ - $\beta'$ -carotene; capsorubin from *Capsicum annum* is 5,5'-desoxy- $\alpha$ - $\alpha'$ -fucoxanthin; euglenarhodon of the *Euglena* sp., is 2-2'-4-4'-tetraketo- $\beta$ - $\beta'$ -carotene; rubixanthin from rose hips is 3-hydroxy- $\beta$ -carotene- $\beta'$ -lycopene; and rhodoviolascins from the purple bacteria, *Rhodovibrio* and *Thiocystis*, is 3-3'-dimethoxy- $\Delta^{3,4}$ -dehydro-1'-2'-dihydro- $\beta$ - $\beta'$ -lycopene.

The identification and purification of these compounds is a large field of investigation by itself, and represents one of the triumphs of the chromatographic technique.

The association of carotenoids with chlorophyll in plants suggests a role in photosynthesis, e.g. in controlling the equilibrium between different forms of chlorophyll. They are probably participants of an oxidation-reduction system.

CAROTENOLS

Hydroxy carotenoids, found esterified with fatty acids, combined with sugars or proteins; include rhodopsin, porphyropsin, iodopsin, the vitamins A.

CAROTIN

See Carotene.

CARRAGEEN

Irish Moss; See Mucilages.

## CARR-PRICE REACTIONS FOR VITAMIN A

I. Chloroform-washed and dried antimony trichloride is dissolved in chloroform to make a 30% solution. After standing, the clear solution is decanted and used from a burette. 2 cc. of reagent are added to 0.2 cc. of a 30% solution of the oil in chloroform; a brilliant blue color, unchanged for 3 minutes, is obtained.

II. With stannic chloride in chloroform a deep blue color rapidly changing to purple is obtained.

III. The addition of anhydrous ferric chloride to a chloroform solution of the Vitamin A—containing oil gives rise to a fluorescent reddish-violet color.

IV. A red-violet color fading to brown is obtained when finely powdered anhydrous aluminum chloride is added to the oil.

Addition of a minute trace of aluminum chloride to a solution of oil in chloroform containing dry hydrogen chloride gas or phosgene produces a fine purple color.

Reference: Biochem. J. 20, 397 (1926). Pharm. J. 118, 752, 758 (1927).

## CARTILAGE

Gristle; elastic tissue lining joint surfaces or forming special structures, like the ear.

## CARVACROL

2-hydroxycymene, present in essential oils; b.p. 238°C.

## CARVONE

$C_{10}H_{14}O$ ; d-form chief constituent of dill and caraway; l-form chief constituent of spearmint; a ketone of dipentene.

## CASANOVA REACTION FOR LECITHIN

An ether solution of lecithin is shaken with a 10% aqueous solution of ammonium molybdate and floated on sulfuric acid; a reddish ring is formed which changes to green and then to intense blue. Reference: Boll. chim.-farm. 1911, 309. Apoth. Ztg. 1911, 912.

## CASCARA SAGRADA

Dried bark of *Rhamnus purshiana*, very bitter and used as laxative; active principle is "emodin".

## CASEIN

A phosphoprotein found in the milk of every mammal. It has a particle weight ranging from 75000 to 375000, indicating that it is a reversible dissociable component system. It is a fairly strong acid, probably due to an unesterified H of the phosphoric acid, the esterified group being connected to a hydroxyl group of serine. In the presence of rennin it forms soluble paracasein, which in the presence of  $Ca^{++}$ , forms the insoluble curd  $Ca$  paracaseinate.

## CASTOR OIL

Oil of the seeds of *Ricinus communis*; the purgative effect is due to glyceryl esters of ricinoleic acid.

See Urology.

## CATABOLISM (KATABOLISM)

(Spelling with C more recent but less desirable since syllable is not of Latin but of Greek origin.) The sum of all processes in an organism by which the chemical energy of food or body substance is transformed to other forms of energy, mainly heat. (Break down processes.) M. K.

## CATABOLIZABLE ENERGY

Energy which is available for

animal heat production. Metabolizable energy (see this) minus energy in milk or eggs. M. K.

# CATALASE

There are probably several catalases, although "catalase" of different sources has been crystallized. Nearly all living tissues contain it. It is high in liver and in sprouted seeds. Its biological function is to destroy any accumulation of hydrogen peroxide. Trypsin inactivates it. An anti-catalase may be produced by immunological procedures. The molecular weight of crystalline catalase has been reported as 225,000 to 300,000. Biliverdin may be produced from it by reaction with acetone and HCl. It probably contains 3 molecules of iron porphyrin and 1 molecule of bile pigment Fe porphyrin per molecule. Its absorption bands are at 629, 544 and 506.5 m $\mu$ . and its i.p. is 5.5.

# CATALEPSY

See Epilepsy.

# CATALYSIS

The acceleration positive or negative and possibly the initiation of a reaction, by comparatively small amounts of foreign substances called catalysts, these substances being recoverable unchanged at the end of the reaction. The catalyst acts as a source of surface energy for the reaction.

# CATALYST

A substance which changes the rate of a reaction actually in process without being consumed by the reaction.

# CATAMENIA

Menstruation.

# CATAPHORESIS

The migration of the colloidal

micelle, through the dispersion medium, due to an imposed e.m.f. on the micellar particle.  
See Protoplasm.

# CATARACT

See Eye, Biochemistry of.

# CATARRH

The inflammation of the mucous membrane in a cold.

# CATECHOL

Ortho-hydroxyphenol; obtained from catechu dye; m.p. 105°.

# CATECHU

Dried extract of *Uncaria gambier*; used as general astringent and for diarrhea.

# CATGUT

Filaments made from sheep intestines.

# CATHARTOMANNITE

See Senna.

# CATHEMOGLOBIN

The compound of hematin with denatured globin, e.g. produced by denaturation of methemoglobin with chloroform.

# CATHEPSIN

A system of proteolytic enzymes present in animal and bacterial cells generally. It is active in slightly acid solution and contains components which are inactivated by copper salts and iodoacetate and are activated by SH groups and cyanide.  
See Autolysis.

# CATION

A positively charged ion.

# CATIONOGENS

Elements in an unionized state which can become cations in the body.

# CAUL

Amniotic membrane; amnion; omentum.

**CAULOBACTERIALES**

See Microbiology.

**CAULOCALINE**

See Plant Growth Hormones.

See Phytohormones.

**CELLASE**

See also Enzymes, Non-Proteolytic.

**CELLOBIASE**

See Cellulose Decomposition, Enzymes, Non-Proteolytic.

**CELLOBIOSE**

$C_{12}H_{22}O_{11}$ ; a reducing disaccharide, 4-(Beta-D-glucosyl)-D-glucose, prepared by acetolysis of cellulose followed by deacetylation of the resulting octaacetate.

**CELL PARTS**

See Biophysics.

**CELLS, ARTIFICIAL**

See Protoplasm.

**CELLULAR PULSATION**

See Protoplasm.

**CELLULASE**

A polyase which splits cellulose, found in *Helix pomatia*.

See Enzymes, Non-Proteolytic, Cellulose Decomposition.

**CELLULOBACELLUS**

See Cellulose Decomposition.

**CELLULOMONAS**

See Cellulose Decomposition.

**CELLULOSE**

$(C_6H_{10}O_5)_x$ ; a polysaccharide composed of  $\beta$ -D-glucopyranoside units. It forms the cell walls and fibrous structure of many plants, and is the chief constituent of paper and wood. It is insoluble in water and organic solvents but dissolves in ammoniacal copper solutions (Schweizer reagent) forming complex ions from which it may be regenerated by means of acid; it

dissolves also in a mixture of alkali and carbon disulfide forming xanthogenates from which it is regenerated by the addition of acid to give various materials such as rayon and Cellophane. Cellulose esters and ethers are widely used in plastics, lacquers and explosives, and as artificial silk, viscose, nitrocellulose, gun-cotton, celluloid.

**CELLULOSE DECOMPOSITION BY MICRO-ORGANISMS**

The utilization of cellulose by micro-organisms takes place under a wide range of circumstances and is in general an uncontrolled, though not necessarily undesirable process. Its economic implications are great and many problems in this field remain to be solved. Decomposition almost always takes place under conditions that permit of its attack by a mixed microbial population and most usually the substrate is not exclusively cellulosic. As a result it is not easy to assess the role played by any individual organism, and pure cultural studies may be misleading in that such a condition is in fact abnormal.

Some distinction can be made, however, between those processes in which substantially pure cellulose is attacked, and those in which cellulose is the major constituent, not alone but accompanied by other, usually more available, plant constituents.

Microbial attack on pure cellulose is in practice frequently undesirable, but rarely proceeds to completion in the sense that much of the cellulose is fully decomposed. More usually the attack is manifest by spoilage of appearance or loss of strength. Paper is subject to dis-

coloration as the result of fungal activity, and many common fungi can develop slowly on paper if the moisture conditions are suitable. The attack may be accelerated by the use of sizes or finishes of an available nature. Fibres such as cotton, flax, etc., are subject to considerable damage by "mildewing" if improperly stored, and again fungi are mainly responsible since they are capable of growing at low moisture levels. Textile fabrics similarly may be damaged by microbial attack and loss of strength may be more serious than pigmentation. Rot-proofing of fabrics or cordage exposed to moist conditions is designed primarily to prevent the initiation of such attack. In the last decade innumerable uses have been found for cellulose derivatives, particularly the esters and ethers. One of the valuable characteristics of these compounds is their greater resistance to microbial spoilage under ordinary circumstances. While it may appear that the utilization of pure cellulose by micro-organisms is generally an undesirable process, many attempts have been made to develop controlled fermentation processes that would yield products of commercial value. Wood pulp has usually been regarded as the most promising form of cellulose for this purpose, and certain anaerobic bacteria the most suitable agents in view of the vigor of their attack and the incompleteness of the oxidation accomplished. The direct products are fatty acids, ethyl alcohol, carbon dioxide and hydrogen, with methane frequently formed by a secondary process. The yields of acids, however, have not been too encouraging and the economic feasibility of the process is questionable. In some sewage disposal plants the combus-

tible gases which arise in part from cellulose are employed as a source of power. Fermentation products have been obtained indirectly from cellulose after preliminary hydrolysis with acid, as in the Bergius process but the organisms then employed do not have to have the property of attacking cellulose.

Microbial attack on the cellulose of plant materials occurs in innumerable natural transformations, which are usually more complex than may appear at first sight owing to the heterogeneity of the substrate and the variety of environmental conditions encountered. Cellulose is utilized microbially in the digestive tract of herbivorous animals and in insects; cellulose is decomposed in soil as natural vegetation and crop residues decay and are incorporated; cellulose is decomposed in compost piles and manure heaps; cellulose is decomposed in marshes and swamps, and in rivers and lakes; cellulosic walls in living plants are penetrated by the action of pathogenic organisms, and in woods disintegrated by wood-decomposing fungi. In almost all these natural processes the cellulose is the constituent which suffers the greatest loss, and the removal of the cellulose is the change which produces the most significant alterations in the properties of the plant material concerned.

In the study of the microbiological utilization of cellulose, information of two kinds is needed. Firstly, there must be available some means of following the changes produced in the cellulose, and secondly, there must be available methods of recognition of the active organisms. The former, insofar as the overall changes are concerned, is the easier; the latter, involving as it does the



isolation, separation, and culture of the organisms is the more difficult.

Cellulose is wholly insoluble in water, and accordingly in those cases in which substantially pure cellulose is appreciably attacked, the loss in weight after washing may be used quantitatively. If gummy or mucilaginous synthetic products are produced by the organism, dilute carbonate or ammonia may be used to aid removal. The determination of the extent of attack on fibers, fabrics, and paper is more difficult since the product may be spoiled without extensive and easily visible decomposition. In such circumstances microscopic methods are ordinarily employed. Tendered fabrics and fibers treated with dyes such as congo red and methylene blue color more intensely than unattacked materials. The behavior on swelling with strong alkali or with alkali and carbon disulphide is abnormal, and microbial damage can be distinguished from that produced chemically by these means.

The determination of the extent of attack undergone by the cellulose of plant materials is made usually by isolation of the cellulose by some modification of the Cross and Bevan procedure. Alternate chlorination and extraction with hot neutral sulphite results in the removal of associated cell wall constituents, such as the hemicelluloses and lignin. A cellulosic residue similar but not identical in composition may be obtained by direct treatment of the plant material with hot monoethanolamine, and the simplicity of this process has much to recommend it for comparative purposes. An approximate figure may be obtained by a hydrolytic method in which easily hydrolyzable polysaccharides are first re-

moved by treatment with dilute acid, and then the residual cellulose is put into solution in cold 80 per cent sulphuric acid, diluted and boiled to yield glucose, and titrated by any convenient reducing group method. The figure so obtained is lower than that given by direct isolation procedures. The hydrolytic method has the great advantage, however, that it can be used in the presence of soil or other inert material.

Media of two general types are used for the isolation and culture of cellulose decomposing organisms, namely those consisting of some form of purified cellulose, such as filter paper, and those containing regenerated cellulose, or partially hydrolyzed cellulose. Many workers have employed filter paper or cloth laid on the surface of agar or silica gel containing the necessary salts. The paper or cloth is ordinarily moistened with nutrient solution and has to be kept quite moist if good growth is to be obtained. Such media are satisfactory for the original isolation of cellulose-decomposing bacteria in the mesophilic range, but are less satisfactory for the isolation of thermophilic organisms or fungi. Filter paper as a medium does not lend itself well to the normal dilution plating techniques by which authentically pure cultures are ordinarily obtained. Regenerated celluloses, such as those obtained after solution in cuprammonium, or hydrocelluloses obtained by brief treatment with warm strong sulphuric acid, may be incorporated in agar since the effects of the treatments are to destroy the macrofiber structure. The growth of many cellulose organisms on these media is very restricted but adequate for separa-

tion. Cellulose dextrans prepared by the controlled cold acid hydrolysis of cellulose may similarly be employed in agar. Opalescent media are obtained on which active cellulose decomposers make limited colony growth, but inasmuch as the colonies may be surrounded by a clear halo their recognition is easy. Cellulose dextrin media are well adapted to the enumeration of cellulose-decomposing bacteria in soil or sewage, and permit of far more satisfactory comparisons than the dilution method in which presence or absence of growth on filter paper strips is observed.

The ability to attack cellulose is not a property limited to a few highly specialized organisms. Many bacteria, actinomycetes and fungi utilize cellulose to a greater or less degree. The widespread use of pure cellulose, such as filter paper, in isolating and characterizing cellulose organisms has led to over emphasis of the specialized forms and neglect of those organisms which do not develop vigorously on such a highly purified insoluble substrate but which nevertheless do utilize cellulose when it is present with other cell-wall constituents of greater availability.

Among the bacteria, those falling within the anaerobic thermophilic group have perhaps been most studied because of their possible industrial use. The products usually given from cellulose by anaerobic organisms are acetic, butyric, and lactic acids, ethyl alcohol, carbon dioxide and hydrogen, though traces of other alcohols and acids may also be found. Methane, which has long been regarded as a product of the anaerobic dissimilation of cellulose, is probably not directly so, but is rather produced second-

arily by methane organisms which accomplish reduction of carbon dioxide by hydrogen transfer from one of the primary products. The most vigorous thermophilic cultures are more or less stable composites of several organisms, and are best obtained from the dung of a herbivorous animal. Such composite cultures frequently do not give reproducible yields of fermentation products. Purification of such cultures usually results in a loss of fermentative power, and a change in the relative proportions of the several products. The crude culture may consist of several distinct organisms only one of which is capable of accomplishing the initial attack on cellulose. The associated forms are usually facultative and their presence enables the cellulose organism, a strict anaerobe, to be active under aerobic or only partially anaerobic conditions. Several anaerobes, the activity of which is optimum within the unusual range of 38° to 50°, have been isolated from the digestive tracts of man and animals. Best known perhaps are the Khouvine organism, *Bacillus cellulosa*, *dissolvens* and *Plectridium cellulolyticum*.

The rapidity of action of the mesophilic cellulose bacteria is on the whole far less than that of the thermophilic forms. Few are limited to cellulose as a source of carbon, and the majority are capable of utilizing slowly and incompletely a wide range of carbohydrates. Many short rods with rounded ends have been described and placed in the genus *Cellulomonas*. Other curved rods with similar properties have been classified as belonging to the genus *Cellvibrio*. Most attention has been directed to the cytophagas, that are widely distributed in soil.

This is due partly to their specialized character, and partly to their remarkable morphology. The type species was incorrectly named *Spirochaeta cytophaga* because of its spirochaete-like appearance. Young cultures on filter paper consist of long, thin, flexuous rods, tapering or pointed at the ends. The cell wall is not rigid and the cell may move by a peculiar flexing movement. This is sufficient to exclude the group from the true bacteria. Older cultures may contain in addition a large coccus, which in fact is a sporoid or microcyst, and not a coccoid contaminant as has been maintained by as great an authority as Winogradsky. Species exist both with and without the microcysts. It is probable that the cytophagas should be included under the order Myxobacteriales. Cytophagas that utilize cellulose only feebly but attack a wide range of other compounds have been isolated from marine sources. It is clear that all species of this organisms are not obligate cellulose decomposers, and even the soil forms, that have been said to be so, can utilize the predominantly pentose-containing cellulosans that are associated with the cellulose of most angiosperms more readily than the long-chain cellulose fraction. Most mesophilic cellulose bacteria are highly aerobic and few facultative or anaerobic forms are known though they must undoubtedly exist. Aerobic spore-formers have been described under the genus *Cellulobacillus*, but the justification for the creation of new genera on the basis of cellulose-decomposing ability alone is questionable.

The list of fungi capable either of growing on pure cellulose or attacking the cellulose of plant

materials is a very long one. Many are more vigorous in the latter circumstances than in the former. Ample available nitrogen must be present because the synthetic abilities of fungi are far greater than of bacteria. As much as one-third the carbon utilized from cellulose may be present in the microbial tissue formed. A deficiency of nitrogen retards the rate of decomposition. There is some evidence that in soil, fungi may be more vigorous than bacteria in the decomposition of the cellulose of added plant material and that a fungal attack precedes a bacterial attack. Sequential changes in the population are an inevitable result of substrate heterogeneity. Single fungi do not seem able to accomplish either so rapid or so extensive removal of cellulose from plant materials as mixed populations of fungi and bacteria. Some fungi can develop at relatively low moisture levels and are responsible for "mildewing" of fabrics and paper. Growth in such circumstances is usually very restricted and the damage is often limited to a deterioration in strength, and staining due to the color of the fungal growth. The cellulose of dead limbs on trees, and intact lumber is utilized slowly by the higher fungi or Basidiomycetes that seem peculiarly adapted to the penetration of lignified walls and growth under conditions of relatively low moisture content and poor air supply. Certain of these are highly efficient in the assimilation of available nitrogen. All seem to use other cell wall constituents along with the cellulose.

The information as to the biochemistry of the process of cellulose decomposition is far from satisfac-

tory. The conventional view is that by means of an exo-enzyme system hydrolysis of the cellulose to glucose is effected, and this glucose is then dissimilated intercellularly. If the structure of cellulose is represented by a simple long chain molecule the primary attack could be accomplished by a hydrolytic system that split off terminal glucose units from the long chains. Such a process would not be accompanied by the production of any considerable amount of cellulose dextrin. However, there is a strong probability of some kind of cross-linkage between chains and therefore the hydrolytic system is probably more complicated. Arguing by analogy with starch it has been often suggested that the disaccharide cellobiose may be produced in the hydrolysis of cellulose and its production has been claimed but not positively verified. To account for this, the existence of two hydrolytic enzyme systems has been suggested, one, cellulase, producing cellobiose from cellulose, and one, cellobiase, producing glucose from cellobiose. Various workers have demonstrated beyond question the presence of reducing substances in aerobic cellulose decompositions, in which the further development of the active organism has been checked either by addition of toluene or reduction in oxygen supply. Not in every case has the identification of the presence of glucose been satisfactory, and that of cellobiose is still questionable. The nature of the intermediate steps is quite unknown. Hydrolytic fragments of cellulose containing several and perhaps as many as 10-15 glucose units are soluble in water and might pass into the cell. Complete extracellular hydrolysis to glucose is not

essential. It seems likely that the primary enzyme system is composite since organisms exist which can utilize the insoluble cellulose dextrin but which cannot develop on cellulose alone. The observation that certain of the more specialized cellulose organisms are inhibited by relatively low concentrations of glucose might suggest that the dissimilation does not normally proceed through this sugar. Other explanations, however, are possible.

The later stages of cellulose decomposition are not much more satisfactorily understood than the primary attack. Various products have been described but accurate balance sheets are few, and indeed the precise nature of the products formed by some of the most commonly recognized cellulose bacteria cannot be found in the literature. In general it seems that the aerobic mesophilic bacteria effect extensive oxidation, so that most of the carbon utilized can be recovered as  $\text{CO}_2$ . No more than a trace of acids, either volatile or non-volatile can be found in cytophaga cultures. In the few cases in which acid production by aerobic organisms has been found the quantity is usually small. Capsular polysaccharides containing uronic groupings are formed by some aerobic mesophilic bacteria. Anaerobic organisms on the other hand give substantial amounts of acidic products and some alcohol. Acetic and butyric acids are commonly formed, though good yields of formic acid have been reported in one case. The yields of volatile acids are usually in the neighborhood of 50-60 per cent of the cellulose fermented. Non-volatile acid and alcohol are produced only in relatively small amounts. It is unlikely that alcohol

production could be increased beyond 10-15 per cent of the substrate removed. Almost nothing is known of the products of decomposition of cellulose by fungi. From sugars many fungi produce appreciable quantities of the di- and tri-basic non-volatile acids, and rarely more than traces of volatile acids. However, none of the former have been reported as being produced from cellulose despite the probability of their formation.

Some of the unsolved problems connected with the utilization of cellulose by micro-organisms have been indicated above. From a theoretical viewpoint undoubtedly the most important is that of the nature and mode of action of the enzymes responsible for the initial phases of cellulose breakdown. It appears that the exo-enzyme responsible is not produced particularly freely, which is perhaps not surprising in view of the fact that the substrate is wholly insoluble. Fungi may be a better source than bacteria. It is not known whether a phosphorylation mechanism is involved, though this should be capable of ready determination. From a practical viewpoint a second problem, which has ramifications through many of the natural processes in which cellulose decomposition occurs, is the effect of the presence of other constituents on the availability and utilization of the cellulose. The cell walls of mature materials may be predominantly cellulosic but they are also incrustated and infiltrated with more available polysaccharides such as the polyuronide hemicellulose and cellulosans, and less available material in the form of lignin. The relative proportions of these three major component changes with age.

Increasing lignin content is usually accompanied by increasing resistance to decomposition in *in vitro* experiments, yet cellulose cannot be detected in the organic fraction of soil which is largely derived from the decomposition of partially lignified materials. Relating to this general question of mixed substrates is the effect of composite cultures. The association of organisms of entirely different characteristics, such as bacteria and fungi seems to be particularly effective in dealing with the composite substrates provided natural materials. Not far removed from the same problem is the whole subject of the biochemistry of the digestion of cellulosic materials by herbivorous animals, a process which is to a considerable extent microbial. The cellulose of roughages is ordinarily quite incompletely utilized, and great wastage in fact occurs.

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#### BIBLIOGRAPHY

Many references to the original literature may be found in the three following publications:

A. G. Norman and W. H. Fuller—

Cellulose decomposition by micro-organisms. *Advances in Enzymology*, 2: 239, 1942.

A. C. Thaysen and H. J. Bunker—

The microbiology of cellulose, hemicelluloses, pectin and gums. London, 1927.

S. A. Waksman—

The microbiology of cellulose decomposition and some economic problems involved. *Bot. Rev.*, 6: 637, 1940.

#### CELLULOSE, TEST FOR

See Cross-Bevan.

#### CEMENTUM

See Teeth, Biochemistry of.

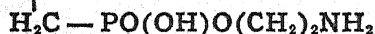
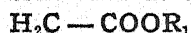


## CENOZOIC ERA

The era of mammals; includes the recent, pleistocene, pliocene, miocene and eocene; about 3 million years.

## CEPHALIN

Any one of a group of phosphatides found in animal and plant cells, particularly in brain and nerve tissues. It is soluble in water and most organic solvents except alcohol and acetone:



Where  $\text{R}_1$  and  $\text{R}_2$  are fatty acids.

H. S.

## CEPHALOPODA

See Mollusca.

## CERAMIDES

Compounds which may be looked upon as part of cerebrosides or sphingomyelins, e.g. lignoceryl-sphingosine (kerasin minus galactose) found in lung and spleen.

## CEREBELLUM

See Nervous System.

## CEREAL

Edible grain originating from a grass.

## CEREBRON

Phrenosin.

## CEREBRONIC ACID

$\text{C}_{24}\text{H}_{50}\text{O}_8$ ; an acid, possibly  $\text{CH}_3(\text{CH}_2)_{21}\text{CHOH}\cdot\text{COOH}$ , forming part of the phosphatide sphingomyelin and the cerebroside phrenosin.

## CEREBROSIDASE

An enzyme which splits cerebrosides, liberating ceramides; needs activation by cysteine, glutathione or ascorbic acid.

## CEREBROSIDES

White, wax-like organic compounds found in the brain and nervous tissues with the phosphatides. They consist of one molecule of a  $\text{C}_{24}$  or  $\text{C}_{25}$  fatty acid, with a peptide linkage to a molecule of sphingosine, which is linked to molecule of d-galactose. They are soluble in most organic solvents except ether and alcohol.

## CEREBROSPINAL FLUID

A clear, colorless liquid bathing the spinal column and the brain, pH 7.4. It is a blood plasma dialysate, chemically modified by the choroid plexus epithelium.

## CEREBRUM

See Nervous System.

## CERINIC ACID

See Cerotic Acid.

## CEROLIN

An alcoholic extract of brewer's yeast of indefinite composition.

## CEROTIC ACID

A saturated fatty acid,  $\text{CH}_3(\text{CH}_2)_{24}\text{COOH}$ , found in beeswax, opium wax, wool fat; m.p.  $82.5^\circ\text{C}$ .

## CERUMEN

(1) Yellow wax of ear.

(2) Wax of stingless bees.

## CERUMINOUS GLANDS

Wax producing ear glands.

## CESTODES

Tape-worms; platyhelminths.

## CETACEUM

See Spermaceti.

## CETACEANS

Marine mammals, e.g. whales.

## CETOLEIC ACID

An unsaturated fatty acid,  $\text{C}_{22}\text{H}_{42}\text{O}_2$ , with one double bond, found in marine animal and fish oils.



**CETYL ALCOHOL**

Hexadecanol, m.p.  $49^{\circ}$ , which as palmitate is chief constituent of spermaceti.

**CEVADINE**

See Veratrine.

**CEVITAMIC ACID**

See L-Ascorbic Acid; vitamin C.

**CHABROL-CHARONNET**

**TESTS FOR BILE SALTS**

I. Four cc. of a solution of the substance in 10 cc. 85% phosphoric acid are heated in a boiling water bath for 4 minutes, cooled, and treated with 1 cc. 0.6% aqueous vanillin solution; a rose-red color indicates a positive test.

II. Four cc. of serum are treated with 36 cc. 90% alcohol and filtered after which 20 cc. are evaporated below  $60^{\circ}$ , the residue dissolved in 8 cc. phosphoric acid and heated in a water bath for 4 minutes. A rose-red color is obtained with 1 cc. 0.6% aqueous vanillin solution.

Reference: Compt. rend. soc. biol. 115, 834, 838 (1934).

**CHAETA**

Spines or bristles of worms.

**CHARA**

See Bioelectric Potentials.

**CHARLES' LAW**

The volume of a given mass of a gas at constant pressure is increased by  $1/273$  of its volume at  $0^{\circ}$  C. for each degree rise in temperature.

**CHAULMOOGRA THERAPY**

See Chemotherapy.

**CHAULMOOGRIC ACID**

$C_{18}H_{32}O_2$ ; a cyclic fatty acid found in Chaulmoogra Oil which is used in the treatment of leprosy; crystallizes as leaflets from alcohol; m.p.  $68^{\circ}\text{C}$ .

**CHELIDONIC ACID**

A crystalline acid,  $C_8H_8O_2$   $(\text{COOH})_2$ , found in the celandine and white hellebore.

**CHEMICAL BIOLOGY**

See Biochemistry (Definitions).

**CHEMIOTAXIS**

See Chemotaxis.

**CHEMOBIOLOGY**

See Biochemistry (Definitions).

**CHEMOSYNTHESIS**

See Photosynthesis.

**CHEMOTAXIS**

Chemiotaxis; chemotropism; reaction to chemical gradients, such as found in solutions.

**CHEMOTHERAPY**

Chemotherapy is the science of treating infectious diseases by specific chemical compounds which exert their action systemically. The three factors involved are the infectious agent, the chemical substance and the host or organism.

The subject had its beginning with the discoveries that cinchona bark was valuable in curing malaria; ipecac in treating amebic dysentery; and mercury in the therapy of syphilis. The modern science of chemotherapy commenced with the research of Paul Ehrlich, who systematically prepared and tested a long series of organic arsenic compounds for their trypanocidal efficacy. As a guiding principle he employed the curative ratio which is the minimum lethal dose (or tolerated dose) divided by the minimum curative dose. He set 3 as the safe ratio. Ehrlich found that salvarsan (also known as 606 and now as arsphenamine) was the most effective compound against syphilis. Later he prepared neo-salvarsan which has the advantage of being water soluble and neutral.

Following Ehrlich's epochal discovery many advances were made concerning the treatment of spiriochetal, trypanosomal and protozoal infections.

In the treatment of syphilis the arsphenamines have retained their place of importance, but other valuable compounds have been added. Mepharsen is particularly effective. Tryparsamide is valuable in the treatment of central nervous system syphilis. Bismuth salts are important as antiluetic agents and have largely replaced mercury in the routine treatment of this important venereal disease.

Quinine remains the most important agent in the treatment of malaria, but a number of synthetic compounds, notably atabrine and plasmochin are also employed in the control of this disease. Amebiasis is combated with emetine (obtained from ipecac) and several synthetic products such as chinofon, vioform and carbarsone.

The treatment of the dreaded disease of leprosy by chaulmoogra oil offers real promise. The active principles are two unsaturated fatty acids, chaulmoogric and hydrocarpic. Leishmaniasis (kala azar and oriental sore) and bilharziasis are successfully treated with antimony. The oldest compound of this element used in therapy is tartar emetic. Several new derivatives have recently been introduced, namely antimony sodium thioglycollate, antimony thioglycollamide, and fuadin.

While the chemotherapy of diseases caused by spirochaetes, trypanosomes and other protozoal parasites steadily advanced, the treatment of bacterial diseases with chemical agents proved unsuccessful

and discouraging until Domagk in 1935 discovered that prontosil, an azo dye, protected mice against streptococcal infection. The successful use of this dye against hemolytic streptococcal infection in humans was quickly established. At the Pasteur Institute in Paris it was found that in the body the dye, prontosil, splits at the azo linkage and yields p-amino-benzene sulfonamide (sulfanilamide), which proved to be the active chemotherapeutic agent. The great effectiveness and specificity of sulfanilamide against various bacterial diseases was soon established, but its limited value against certain organisms, particularly the pneumococci, soon became apparent. This led to a quest of substituted sulfanilamides. The most successful of these are sulfapyridine, sulfathiazole and sulfadiazine.

Sulfanilamide is effective against beta hemolytic streptococci, meningococci, gonococci, *C1 welchii*, and several other types of bacteria. Its mode of action is not known. The drug exhibits bacteriostatic action in vitro, but its much greater activity in vivo suggests that the humoral and cellular defense mechanisms of the organism contribute to its efficacy. While sulfanilamide is extremely effective against virulent bacteria, it has a low toxicity for the host. It occasionally causes mild mental symptoms, cyanosis, anemia, neutropenia, fever, and various forms of dermatitis. Rarely, however, are these of a serious nature and the important therapeutic value of the drug far outweighs all its untoward reactions.

Sulfapyridine (2-sulfanilyl aminopyridine) finds its greatest usefulness in the therapy of pneumococcal infections, which resist the action

of sulfanilamide. The compound is much more toxic than the parent drug. Nausea and vomiting are common and often severe. The low solubility of the acetylated compound formed in the body often causes the formation of crystals in the urine and these may obstruct the tract and bring about anuria.

Sulfathiazole is widely used. Like sulfapyridine, it is effective against the pneumococcus, and also against many of the group affected by sulfanilamide. The drug has also been employed successfully against staphylococci. Sulfadiazine is similar in action to sulfathiazole. Although relatively new, it is very promising since it is highly effective, and has a low toxicity.

The sulfonamide drugs have revolutionized the treatment of infectious diseases. Various infections, which prior to these drugs were invariably fatal, respond promptly and effectively to these new chemotherapeutic agents. The mortality of pneumonia has been markedly reduced and meningococcal meningitis, gonorrhea, puerperal sepsis, urinary tract infection and many other common and serious infectious diseases are effectively and promptly cured. In one important virus disease, trachoma, sulfanilamide has been employed with success.

In spite of the brilliant results already obtained, the chemotherapy of bacterial diseases is still in its infancy and it seems not too sanguine an expectation to see marked strides in this field which will dwarf in comparison all present day accomplishments.

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## CHEMOTROPISM

Reaction of a living form to chemicals.

## CHEMURGY

See Agricultural Biochemistry.

## CHENODESOXYCHOLIC ACID

$C_{24}H_{40}O_4$ , m.p.  $140^\circ$ , a bile acid found in man, ox, monkeys, fowl and fish. It is 3, 7-dihydroxy-cholanic acid.

## CHEVALLIER-CHORON TEST FOR VITAMIN A IN BLOOD

Twenty gm. of absolute alcohol are added to a moist-dry mixture of 3 cc. of blood and 20 gm. anhydrous sodium sulfate and the mixture allowed to stand for 1 hour. An absorption spectrum band at 325 m $\mu$  indicates vitamin A.

Reference: Compt. rend. soc. biol. 118, 889 (1935).

## CHIMYL ALCOHOL

Cetyl-alpha-glyceryl-ether, found in liver oils of elasmobranch fishes.

## CHINESE YEAST

Mucor Rouxii, which produces very active amylase when grown aerobically and high concentrations of alcohol on carbohydrate fermentation.

## CHINIC ACID

See Quinic Acid.

## CHINICINE

See Quinicine.

## CHINOFON

See Chemotherapy.

## CHIROPTERA

Placental, flying mammals, e.g. bats.

## CHITIN

A polysaccharide that forms the hard, resistant exo-skeletons of

many invertebrates, and composed of N-acetyl- $\beta$ -D-glucosamine units joined in long chains at carbon 4. On acetolysis it yields octaacetylchitobiose, and on complete hydrolysis "glucosamine" (2-amino-2-desoxy-D-glucose).

#### CHITINASE

Enzyme capable of hydrolyzing chitin, found in moulds and snail digestive juice; produces glucosamine and N-acetyl glucosamine.

#### CHITOBIOSE

$C_{12}H_{23}O_{10}N$ ; an amino-sugar, 2-desoxy-2-amino-4-( $\beta$ -D-glucosyl)-D-glucose, obtained by the partial hydrolysis of chitin in a manner analogous to the preparation of cellobiose from cellulose.

#### CHLAMYDOBACTERIALES

See Microbiology.

#### CHLORAL

Trichloroacetaldehyde, b.p.  $98^\circ$ ; forms a hydrate which is used as soporific and anodyne.

#### CHLORAMINE-T

Sodium toluene-p-sulphonechloramide, a powerful antiseptic.

#### CHLORELLA PYRENOIDOSA

See Photosynthesis.

#### CHLORENCHYMA

Chlorophyll-containing stem tissue.

#### CHLORIDE

#### IMPERMEABILITY

See Electrolyte Balance in Muscle.

#### CHLOROCRUORIN

A dichroitic respiratory pigment of certain polychaetes, e.g. Spirographis. While similar in structure to hemoglobin, the hemin group is not a red hemin as is protohemin but is a pheohemin, containing a formyl group in the 2-position instead of the vinyl

group present in the corresponding position in protohemin.

#### CHLOROCRUORIN

The prosthetic group of chlorocruorin, the respiratory pigment of certain polychaete worms.

#### CHLOROGENIC ACID

A condensation product of quinic and caffeic acid, found in many plants.

#### CHLOROPHYLL

The green coloring matter of plants. Two forms have been isolated, chlorophyll-a, having the empirical formula  $C_{55}H_{72}O_5N_4Mg$  with  $\frac{1}{2} H_2O$ , m.p.  $150-153^\circ$ , and chlorophyll-b, having the formula  $C_{55}H_{70}O_6N_4Mg$ , m.p.  $183-185^\circ$ . Many decomposition products have been isolated, notably phytol which is 3,7,11,15-tetramethyl- $\Delta^{23}$ -hexadecanol. A common heterocycle of both forms is phorbin which is a porphin. The abstraction of Mg and phytol from the two forms of chlorophyll gives two phaeophorbids. The abstraction of phytol leaves chlorophyllids. The structures are strikingly similar to hematin. The synthesis of carbohydrates by plants under the influence of light is supposed to occur through the absorption of the light energy by chlorophyll-a after a dark reaction involving enzymatic reduction to dehydrochlorophyll. A hexose is formed in the dark reaction. The light reaction is a reoxidation with an absorption of energy.

Reference: Willstaetter and Stoll, Investigations on Chlorophyll.

See also Enzymes, Non-Proteolytic.

#### CHLOROPHYLLASE

A specific esterase found in all green plants. It hydrolyzes chlorophyll to chlorophyllide and phytol alcohol.

**CHLOROPHYLLIDS**

See Chlorophyll.

**CHLOROPHYLL, ROLE IN PHOTOSYNTHESIS**

See Photosynthesis.

**CHLOROPLAST**

Microscopic chlorophyll-carrying proteid body in plant cells, present in vast numbers.

**CHLOROSIS, EGYPTIAN**

See Ankylostomiasis.

**CHOLAGOGUE**

Substance which causes emptying of gall bladder, e.g. cholecystokinin,  $MgSO_4$ .

**CHOLAIC ACID**

See Taurocholic Acid.

**CHOLANGITIS**

See Bile Tract Disease.

**CHOLANIC ACID**

A sterol which forms the nucleus of the bile acids.

**CHOLECYSTITIS**

See Bile Tract Disease.

**CHOLECYSTOKININ**

A hormone of the upper intestine which causes the contraction and emptying of the gall bladder.

**CHOLECYSTOTOMY**

Operation on the gall bladder; the organ is opened and closed again without drainage.

**CHOLEGLOBIN**

See Verdohemoglobin

**CHOLEIC ACIDS**

Stable coordinated molecular compounds of desoxycholic acid with fatty acids, ketones, phenols, hydrocarbons and other compounds. The complexes form in the molecular ratios of 1:2, 1:3, 1:6 or 1:8. Previously confused with Desoxycholic Acid.

See Deoxycholic Acid or Desoxycholic Acid.

**CHOLELITHIASIS**

See Bile Tract Disease.

**CHOLEMIA**

An abnormal amount of bile substances in the blood and tissues.

**CHOLEPYRRHIN**

See Bilirubin.

**CHOLERA BACILLI, TEST FOR**

See Koch.

**CHOLERETIC**

A bile stimulant, e.g. secretin, bile salts.

**CHOLESTEROL**

A sterol present in every animal cell and in more concentrated form in gallstones and brain tissue. It contains a branched side chain of 8 carbon atoms attached to  $C_{17}$  of the sterol nucleus, an OH at  $C_3$  and a double bond between  $C_5$  and  $C_6$ . It forms an insoluble digitonide.

**CHOLESTEROLESTERASE**

See also Enzymes, Non-Proteolytic.

**CHOLESTEROL TESTS**

See Burchard, Golodetz, Kahlenberg, Kreis, Larson, Levine-Richman, Liebermann, Myers-Wardell, Salkowski, Steinle-Kahlenberg, Van Zijp, Windaus.

**CHOLIC ACID**

$C_{24}H_{40}O^5$ ; m.p.  $195^\circ$ ; a bile acid found in man and most animals. It is 3, 7, 12-trihydroxy-cholanic acid.

**CHOLIC ACID TESTS**

See Hammarsten, Mylius Reaction.

**CHOLINE**

Trimethyl Beta-hydroxyethyl ammonium hydroxide;  $(CH_3)_3NOH \cdot CH_2 \cdot CH_2OH$ ; a compound whose derivative acetylcholine has an important connection with nerve

impulses. Choline causes a drop in blood pressure. It is formed by the breakdown of lecithin.

See Creatine and Creatinine Metabolism.

Choline has been shown to be "lipotropic," that is, it prevents or cures fatty livers (which may be due to depancreatization or a breakdown in fat metabolism) either in itself or as the active component of lecithin. Betaine and triethylcholine showed similar action. A factor in the effect is the promotion of the formation of phospholipids. Another factor is the transfer of methyl groups in the synthesis of methionine from homocystine and of creatine, or, in general, where labile methyl groups are required. A third factor is the effect on the production of acetylcholine. Various deficiencies due to lack of choline might involve other factors. Rats show a falling of hair and swollen paws, along with signs of muscular weakness. Hemorrhagic kidneys, deficient vagus function, involution of the thymus, disorders of lactation, etc., have been noted. Vitamin B deficiencies shows close resemblances. Thiamin is definitely a contributing factor in the production of certain fatty livers, called "dietary fatty livers." Choline and thiamin show an antagonism in such cases. That labile methyl groups serve a useful function is shown by the fact that methionine, a source of labile methyl groups, behaves like choline in the removal of some of the above mentioned symptoms. Choline present in ester form is acted upon by the enzyme cholinesterase which has turned out to be inhibitable by thiamine, according to still fragmentary work. Choline itself may derive its methyl groups from other methylated compounds,

e.g. methionine. The most plausible source of the rest of the structure is aminoethanol. As a carrier of labile methyl choline acts as a detoxifying agent, e.g. of pyridine and nicotinic acid, by trans-methylation.

#### CHOLINE DEHYDROGENASE (LIVER)

A cytochrome-reducing dehydrogenase which catalyzes the aerobic oxidation of choline to the corresponding aldehyde.

#### CHOLINERGIC

Pertaining to nerves that liberate an acetylcholine-like substance on stimulation.

#### CHOLINESTERASE

See also Enzymes, Non-Proteolytic.

#### CHOLINE TESTS

See Brieger, Mott-Haliburton, Rosenheim, Sanchez, Schoorl.

#### CHONDRIFICATION

Formation of cartilage.

#### CHONDROITIN SULFURIC ACID

One of the two carbohydrate complexes associated with the protein of the mucins.

#### CHONDROSAMINE

Amino-galactose.

#### CHONDRO-SULFATASE

A special sulfatase which splits chondroitin sulfuric acid.

#### CHORDATA

Protochordata:

Animals with a spinal column, include:

Tunicata—see squirts

Enteropneusta

Cephalochorda—lancelets (Amphioxus).

Vertebrata:

Cyclostomata—lampreys



**Pisces (fishes)**

Elasmobranchii — dogfish,  
shark, ray, teleostei, bony  
fishes

Amphibia—newts, frogs

Reptilia—turtles, lizards, snakes

Aves—birds

Mammalia—mammals.

**CHOROID**

See Eye, Biochemistry of.

**CHORION**

Outer membrane in pregnant  
mammals which encloses the  
amnion and the embryo.

**CHROMATIN**

A protamine nucleate; the nature  
of the link between the prota-  
mine and the nucleic acid is not  
clear, but it is either a salt or a  
coacervate. Chromosomes are  
composed of chromatin.

See Genetics, Biochemical.

**CHROMATOGRAPHIC  
ADSORPTION**

The name applied to the phenom-  
enon of selective adsorption ob-  
served when solutions of certain  
mixtures are passed through a  
column of an adsorbent. It is  
found that one component sepa-  
rates in a ring, below which is a  
ring with no adsorbed substance,  
followed by a ring of a second  
substance, etc. This method is  
useful in separating mixtures of  
closely related compounds.

**CHROMODORIN**

The purple pigment of certain  
molluscs.

**CHROMOGEN**

Any chemical group which by it-  
self or when associated with some  
other group imparts color.

**CHROMOGENIC MATERIAL**

See Creatine and Creatinine  
Metabolism.

**CHROMOPHILIC**

Easily stainable.

**CHROMOPHORE**

A group which gives color to an  
organic compound but does not  
necessarily make it a dye.

Examples:  $\text{NO}_2$ ,  $\text{—N=N—}$ .

See Auxochrome.

**CHROMOPROTEINS**

In the American Classification of  
proteins, the chromoproteins are  
conjugated proteins where the  
prosthetic group is colored.

Examples: Hemoglobin, visual  
purple, ovoverdin, flavoproteins.

**CHROMOSOMES,  
BIOCHEMICAL ASPECTS OF**

See Genetics, Biochemical Aspects  
of.

**CHROMOTROPISM**

Response to color stimulation.

**CHRONAXIE (CHRONAXY)**

Latent period between electrical  
stimulus and muscular response.

**CHRYSLIS**

Pupa stage of insects.

**CHRYSAROBIN**

Benzene extract of araroba, used  
for skin diseases.

See Crysophanic Acid.

**CHRYSENE**

A colorless aromatic polynuclear  
hydrocarbon, m.p.  $255^\circ$ , found in  
coal tar, usually found with a  
small amount of naphthalene which  
gives the commercial chrysene its  
yellow color.

**CHYLE**

The milky emulsion of fat in the  
lymph after absorption from the  
intestine into the lacteals on the  
way to the blood stream.

**CHYLOMICRONS**

Fat droplets in the blood, 1 mi-  
cron or less in diameter. Their  
number increases greatly during  
fat absorption after a meal.

**CHYMASE**

See Rennin.

**CHYME**

The semi-liquid food discharged from the stomach into the duodenum, after the stomach has done its part in grinding and preliminary digestion.

**CHYMOINHIBITOR**

A term introduced by Tauber for substances that inhibit the milk coagulating power of proteases; found in gastric and intestinal mucosas.

**CHYMOSIN**

See Rennin.

**CHYMOTRYPSIN**

A crystallizable proteinase of the pancreatic secretion effective in slightly alkaline media. It has strong milk clotting power. It exists in the pancreas in an inactive form, chymotrypsinogen, which is converted to chymotrypsin by active trypsin, but not by enterokinase.

**CICATRIX**

The fibrous tissue of a scar.

**CICATRIZATION**

See Wound Healing.

**CILIARY BODY**

See Eye, Biochemistry of.

**CILLIA**

See Hair.

**CINCHOL**

$C_{29}H_{50}O$ ; a sterol with one double bond, present in cinchona bark.

**CINCHONA**

Dried bark of Cinchona, used medicinally for fevers and as a tonic, whose active constituents are alkaloids, such as quinine, cinchonidine, cinchonine and quinidine.

**CINCHONA ALKALOID TESTS**

See Deniges.

**CINCHONIDINE**

An isomer of cinchonine, used like quinine;  $C_{19}H_{22}ON_2$ .

**CINCHONINE**

Alkaloid of cinchona, used like quinine; dextrorotary,  $C_{19}H_{22}ON_2$ .

**CINCHOPHEN**

A synthetic 2-phenylquinoline-4-carboxylic acid, used for rheumatism and fever; likely to attack liver; atophan; phenoquin; quinophan.

**CINEOLE**

Eucalyptol; cajuputol; present in many essential oils, m.p.  $-1^{\circ}$ ; b.p.  $174.4^{\circ}$ ; a constituent of oil of eucalyptus, used as inhalant for colds, etc.

**CINNAMALDEHYDE**

Aldehyde of cinnamic acid; b.p.,  $252^{\circ}$ ; sp.gr.,  $1.049^{20}/_4$ ; use as of oil of cinnamon medicinally.

**CINNAMIC ACID**

$C_6H_5 \cdot CH:CH \cdot COOH$ ; m.p.  $133^{\circ}$ ; b.p.  $300^{\circ}$ ; from storax, balsam, cinnamon oil; used as antiseptic, antitubercular.

**CIRRHOSIS, PORTAL OR BILIARY**

See Liver Cirrhoses.

**CITRAL**

A terpene aldehyde,  $C_{10}H_{16}O$ , a constituent of lemon-grass oil and others, a mixture of isomerides of which one is geranial and the other neral; has pleasant odor.

**CITRIC ACID**

A constituent of many juices, especially lemon (5% or more); tribasic acid  $C_6H_8O_7$ , or hydroxytricarballic acid; m.p.  $153^{\circ}$  anhyd., but adds 1 molecule of water; administered for gout and as a purgative in the form of salts; formed by special fermentations.

**CITRIC ACID CYCLE**

See Carbohydrate Metabolism.

**CITRIC ACID TEST**

See Wagenaar.

**CITRIC CYCLE**

Citric acid cycle; theory of Krebs and co-workers to explain catalytic promotion of oxidations in liver, kidney, muscle tissue by citrate, especially in presence of carbohydrates; the stages are: citric, cisaconitic, alpha-ketoglutaric, succinic, fumaric, malic, oxaloacetic, which reacts with pyruvic acid (the metabolite) to reform citric; isocitric acid is probably involved; insulin promotes the reaction still further in vitro, using pigeon breast muscle.

**CITRIN**

Vitamin P.

**CITROMYCETIN**

A yellow pigment from citromyces moulds;  $C_{14}H_{10}O_7$ .

**CITRONELLAL**

l-form found in citronella oil of Java and d-form in citronella oil of Ceylon and eucalyptus oils;  $C_{10}H_{18}O$ , terpene aldehyde.

**CITRONELLOL**

An alcohol  $C_{10}H_{20}O$  of terpene character found in various citronella oils, rose oil, etc.; rhodinol.

**CITRULLINE**

$\delta$ -carbamino- $\alpha$ -amino-n-valeric acid; an amino acid, which according to the criteria of Vickery and Schmidt is not accepted as a proven protein constituent; it has been reported to have the power to increase the rate of urea formation by liver slices.

**CLEIDOIC**

A term applied to eggs provided with water and a protective membrane against its loss, an adapta-

tion alternative to the young being born in the mother (viviparity).

**CLIMACTERIC**

Period of the cessation of full sex functions, as menstruation.

**CLIMACTERIC, MALE**

See Urology.

**CLINICAL APPLICATIONS OF BIOCHEMISTRY (HISTORICAL)**

We are inclined to think of Clinical Biochemistry as a new field because of the great advances which have been made during the past thirty years. However, nothing could be further from the truth; the chief thing that is new is the name.

Nearly all the pioneers in the field of chemistry were attracted to a study of the processes and products of life, although their pupils followed leads which led to the development of pure chemistry. Among these pioneers may be mentioned Lavoisier, Scheele, Dumas, Liebig and Wöhler in particular.

Lavoisier's interest in what we now call biochemistry and clinical biochemistry is illustrated by a statement he made in his last communication (1790) to the French Academy of Science,<sup>1</sup> viz.: "Up to the present time we have learned only to conjecture as to the cause of a great number of diseases and as to the means of their cure. Before hazarding a theory we propose to multiply our observations and to analyze the blood both in health and disease."

On November 15, 1821 Dumas, the teacher of Pasteur, read a now famous paper in collaboration with Prévost before the Society of Physics and Natural History in

Geneva (published 1823)<sup>2</sup> in which they demonstrated that, when the kidneys were removed in cats and rabbits, urea rose to a high concentration in the blood, thus proving that urea was not formed in the kidney as had previously been supposed. The clinical term uremia resulted from these experiments.

One has to read only a few of the early papers by Wöhler and Liebig in the journal they founded, popularly known as Liebig's *Annalen*, to appreciate their keen interest in the intricacies of life. It was in 1828 that Wöhler broke down the barrier between the products of living and inorganic matter, by the conversion of ammonium cyanate to urea (synthesis of urea). It is quite evident that the earlier workers in this field coined the name organic chemistry to apply to what we now call biochemistry, but their pupils, in the extended study of carbon compounds which developed, appropriated the name.

Clinical Biochemistry, or Pathological Chemistry, as it is sometimes called, probably owes more to Felix Hoppe-Seyler than anyone else. In 1856 Hoppe-Seyler was appointed prosecutor and chief of the chemical laboratory of the new pathological institute at Berlin under Rudolf Virchow. Although Hoppe-Seyler had had excellent chemical training, he was also stimulated in his chemical work by Virchow, whose papers indicate he was a first class clinical biochemist. While Hoppe-Seyler's early papers published chiefly in Virchow's *Archiv*, were largely on anatomical topics, there was a gradual shift to chemical topics. In 1864 he was called to Tübingen as the first professor of physiological chemistry in Germany, removing to Strassburg in 1872. Two years after

his first appointment at Berlin (1858) he brought out the first edition of his *Handbuch der physiologisch- und pathologisch- chemischen Analyse*,<sup>3</sup> which went through many editions. This was the bible of the laboratory of clinical biochemistry for more than fifty years, although one of Hoppe-Seyler's successors, as chief of the chemical laboratory at the pathological institute in Berlin, E. Salkowski, wrote a very useful smaller book: *Practicum der physiologischen und pathologischen Chemie*,<sup>4</sup> the first edition of which appeared in 1893. The writer recalls using Salkowski's book while working for a brief period in Dr. Christian A. Herter's laboratory in 1906.

It would appear that Herter was the first in this country to fully vision the great importance of chemistry in clinical medicine. In 1891 he secured as chemist for his private research laboratory E. E. Smith, who had just received his Ph. D. degree in physiological chemistry under Professor Chittenden at Yale. Later he appointed A. J. Wakeman and H. D. Dakin to his staff. Herter was professor of pathological chemistry at the University and Bellevue Hospital Medical College from 1898 to 1903. In 1902 he published his text on chemical pathology.<sup>5</sup> His conviction of the great importance of chemistry to medicine led to his founding in 1905 in collaboration with J. J. Abel the *Journal of Biological Chemistry*. This has now become largely a journal of pure rather than applied biochemistry, but Herter's plan for the *Journal* is indicated in the appreciation which appeared in the *Journal*<sup>6</sup> after his death: "The scope of the *Journal* was to include researches of a purely

chemistry cannot be achieved without simple, delicate and reliable methods. To the American biochemists, Folin, S. R. Benedict and D. D. Van Slyke in particular, this practical specialty of biochemistry owes the development of a great range of useful methods, now in daily use in every up-to-date hospital and clinical laboratory in the world. While Folin and Benedict developed clinical biochemical methods and left their application largely to others, Van Slyke had the opportunity at the Hospital of the Rockefeller Institute for Medical Research to utilize practically the numerous methods he had the ingenuity to develop, of which his gasometric methods are the most noteworthy.

The present author was appointed professor of pathological chemistry at the New York Post-Graduate Medical School and Hospital in 1912 and had the opportunity of following practically this monumental, and chiefly American, development, the larger part of which was devoted to the blood and urine.

With the rise of biochemistry in this country, and later with the great developments in the field of clinical biochemistry, the need of a counterpart to Hoppe-Seyler's Handbuch became evident. This was partially met by the publication by Hawk<sup>7</sup> in 1907 of his text-book on Practical Physiological Chemistry. Although this book was written primarily as a laboratory manual, the author also included the more important useful methods of clinical biochemistry. Twenty-five years later (1932) Peters and Van

Slyke<sup>8</sup> brought out their text on Quantitative Clinical Chemistry, Volume II. Methods, in which is given a detailed description of a large number of the quantitative chemical methods employed in the clinical laboratory.

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#### REFERENCES

<sup>1</sup> Lavoisier, A. L. Quoted by Lusk, G. in A History of Metabolism. Endocrinology and Metabolism. New York, 1922. Vol. 3, p. 28.

<sup>2</sup> Prévost, J. L., and Dumas, A. Examine du sang et de son action dans les divers phénomènes de la vie. Ann de chim. et de phys., 1823, 23: 90.

<sup>3</sup> Hoppe-Seyler, F. Handbuch der physiologischen und pathologisch-chemischen Analyse für Ärzte und Studierende. Berlin, 1858.

<sup>4</sup> Salkowski, E. Practicum der physiologischen und pathologischen Chemie. Berlin, 1893.

<sup>5</sup> Herter, C. A. Chemical Pathology, Philadelphia, 1902.

<sup>6</sup> J. Biol. Chem., 1910-11, 8: 438.

<sup>7</sup> Hawk, P. B. Practical Physiological Chemistry. Philadelphia, 1907.

<sup>8</sup> Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Volume II, Methods. Baltimore, 1932.

#### CLOACA

Common outlet for excretion and sexual products in lower vertebrates.

#### CLONE

An asexually produced individual.

#### CLONUS

A series of distinct muscular spasms.

#### CLOSTRIDIUM BUTYRICUM

See Microbiology.

#### CLOTTING

The formation of an insoluble,

stringy mass of blood, tending to prevent further bleeding. One theory of clotting is: the injury causes cephalin to be liberated from the platelets. This neutralizes heparin, which then allows prothrombin to be converted to thrombin. The latter then converts fibrinogen into insoluble fibrin.

Another theory: Prothrombin is converted to thrombin by an enzyme formed from Ca and blood platelets. The thrombin then converts fibrinogen to fibrin.

#### CLUPADONIC ACID

An unsaturated acid found in many fish oils,  $C_{22}H_{34}O_2$ .

#### CLUPANODONIC ACID

An 18-carbon fatty acid with four double bonds, found in Japanese sardine oil.

#### CLUPEINE

A protamine from herring roe.

#### COACERVATION

The separation of microscopic liquid droplets when sols of two hydrophilic colloids of opposite electric charge are mixed. This appearance of a new phase is a special case of mutual precipitation. Biologically nucleoproteins may be an illustration of the formation and redispersion of "coacervates."

#### COAGEL

See Gel.

#### COAGULASES

See Microbiology.

#### COAGULATED PROTEINS

In the American Classification of proteins, those insoluble primary protein products that are formed from proteins by heat or alcohol.

#### COCA

Dried leaves of *Erythroxylum*

*coca* and *Erythroxylum* *truxillense* exerting stimulant action because of cocaine, its derivatives and truxilline alkaloids.

#### COCAINE

$C_{17}H_{21}O_4N$ ; toxic alkaloid of *Erythroxylum Coca*, methylbenzoylecgonine, monoclinic prisms from alcohol, m.p.  $98^\circ$ , sl. sol. cold  $H_2O$ , giving an alkaline solution. Its hydrochloride, m.p.  $200-2^\circ$ , has been used in medicine as a local anesthetic, but is being replaced by new synthetics. Large doses cause death due to paralysis of the respiratory center.

#### COCAINESTERASE

See Enzymes, Non-Proteolytic.

#### COCAINE TEST

See Young.

#### COCAMINE

See Truxilline.

#### COCARBOXYLASE

Diphosphothiamine; thiamine pyrophosphate; required for the activity of carboxylase, which catalyzes the decarboxylation of pyruvic acid or alpha keto acids. Except in the blood plasma it is present in tissues along with thiamin. It affects carbohydrate metabolism, carbohydrate synthesis and even synthesis of fat from carbohydrate. It is responsible for acetylations, e.g. formation of acetylcholine.

#### COCCERIC ACID

$C_{31}H_{62}O_8$ ; a saturated monohydroxy fatty acid found in Cochineal wax.

#### COCCIDIA

Protozoan parasites which often prey on experimental animals, e.g. the rabbit.



**COCCULIN**

See Picrotoxin.

**COCCUS**

See Microbiology.

**COCCYX**

Several vestigial vertebra of the tail in man.

**COCHLEA**

Organ of hearing in the internal ear.

**COCOSITOL**

See Scyllitol.

**CODEINE**

$C_{18}H_{21}O_3N$ ; orthorhombic prisms with one  $H_2O$ , anhyd. m.p.  $155^\circ$ ; methyl ether of morphine; alkaloid of opium. Resembles morphine in action, but less toxic, less depressing, and slightly more stimulating, causing restlessness in large doses. Fatal dose, over 4.5 grains.

**CODEINE TESTS**

See Aloy-Valdiguie.

**COD LIVER OIL TEST**

See Liebermann-Vogt.

**COELENTERATA**

Class of jelly fishes, corals, sea anemones.

**COELENTERATES**

Invertebrates of the jelly fish type.

**COENZYME**

A low molecular weight material which activates an enzyme; not as completely specific as a kinase.

**COENZYME I**

See Cozymase.

**COENZYME FACTOR**

See Straub Flavoprotein (heart).

**COENZYME-LINKED REACTIONS**

Reactions in a mixture of two enzyme systems in which a single coenzyme undergoes a reduction by one system and an oxidation

by the other, e.g. beta-hydroxybutyrate and acetoacetate and its enzyme, alcohol and acetaldehyde and its enzyme, and coenzyme I.

**COENZYME (Warburg and Christian)**

Coenzyme II; a thermostable substance, composed of 1 molecule of adenine, 1 of nicotinamide, 3 of phosphoric acid and 2 of pentose, which is reduced in the activity of the enzyme of fermentation or of the oxidation of glucose-6-phosphate.

**COFFEARIN**

See Trigonelline.

**COLCHICINE**

$C_{22}H_{05}O_6N$ ; a levorotatory alkaloid of the meadow saffron; administered with belladonna for gout; has shown remarkable use in affecting genetic changes; is the active constituent of the dried corms and seeds of the meadow saffron, known as colchicum. See Agricultural Biochemistry.

**COLE TEST FOR BILE PIGMENTS**

Fifty cc. of the test solution are treated with an excess of lime or baryta water and filtered; the precipitate is treated with 5 cc. alcohol, 2 drops of concentrated sulfuric acid and 3 drops of 50% potassium chlorate solution and boiled. An emerald or bluish-green color in the supernatant liquid indicates bile salts.

Reference: Practical Physiol. Chemistry (1926), 323, 366.

**COLE MICROCHEMICAL REAGENT FOR ALKALOIDS**

Yellow crystalline precipitates are obtained when potassium ferrocyanide is added to solutions of the hydrochlorides of brucine, cinchonidine, cinchonine, cocaine, eucaine, heroin, hydrastine, quino-

line, sparteine, stovaine, strychnine and veratrine.

Reference: Jahresber. Pharm. 1923, 190.

# COLEOPTERA

Beetles with horny front wings under which there are membranous wings.

# COLITIS, ULCERATIVE

See Gastro-Enterology.

# COLLAGENS

A group of albuminoids occurring only in the animal kingdom. They constitute the chief solid matter of white fibrous connective tissue and of the ground substance of cartilage and bone.

# COLLENCHYMA

Thickened plant cells adapted to supporting stem.

# COLLOID

A dispersion of one phase of matter in another, where the particles of the dispersed phase are coarser than molecular. The range of size of colloid particles is arbitrarily fixed between 1 micron and 0.1 micron.

# COLLODION

A solution of cellulose in alcohol-ether. The gel resulting from the evaporation of the solvent is used as a semi-permeable membrane for diffusion, and as an ultrafilter.

# COLLOID GOLD REAGENT

See Zsigmondy.

# COLOCYNTH

Dried pulp of the bitter apple, *Citrullus colocynthis*, which is used for purgative action.

# COLOPHONY

Rosin.

See Resin.

# COLORIMETER

An optical instrument, used in

colorimetric analysis to accurately measure color differences.

# COLORIMETRIC

A method of detection or determination based on a difference, qualitative or quantitative, of color.

# COLOSTRUM

A secretion of the mammary glands found for 2-4 days after the birth of the offspring. Yellowish, viscous, alkaline fluid, with high protein content, acts as a purgative.

# COMMA BACILLUS

See Microbiology.

# COMPARATIVE BIOCHEMISTRY

Comparative biochemistry deals with the differences of chemical composition and metabolism between the various phyla and their subdivisions. General biochemistry and physiology have established the bulk of their facts and laws on the narrow basis of observations and experiments in man and less than a dozen animal species. Comparative biochemistry has hitherto been neglected except for a few selected chapters such as: respiratory pigments, carotenoids, steroids, fatty acids, nitrogen metabolism, water metabolism, reproductive hormones, and certain enzymatic mechanisms. Its systematic study on a phylogenetic basis and correlation with ontogenesis (see Chemical Embryology) remains a challenge to biochemists. (See Comp. Bioch. by Ernest Baldwin, Cambridge 1937; Les correlations humores chez les invertèbres by P. Lélou, Paris 1938). Studies along similar lines in phytochemistry have been pursued by Blagovestchenskii in Moscow.

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**COMPLEMENT,**  
**COMPLEMENT FIXATION**

Lysis of red cells or bacteria by antisera requires the aid of a special agent, present in normal sera and not augmented upon immunization which is called complement or alexin (Bordet Ann. Inst. Past. 10: 193, 1896). It deteriorates slowly on storing and is inactivated by heating, e.g. within half to one hour at 50-60° C.

The characteristic of complement to be bound by the aggregates (precipitates, sensitized cells) formed through the interaction of antigens and antibodies is the basis for a frequently used serological test. In this "complement fixation reaction," introduced by Bordet and Gengou, antigen and antibody to be tested are mixed with fresh normal serum, containing complement, and, after incubation, hemolytic immune serum and the corresponding red cells are added as an indicator. If an immunological reaction takes place in the first stage, complement is fixed and removed from the solution and hemolysis is prevented, completely or in part, according to the intensity of the reaction.

**KARL LANDSTEINER**

From Landsteiner's "The Specificity of Serological Reactions, 2nd Ed., Chas. C. Thomas, Publisher, Springfield, Ill.

**COMPOST**

See Cellulose Decomposition.

**COMPOUND B OF KENDALL**

See Corticosterone.

**COMPOUND H OF REICHSTEIN**

See Corticosterone.

**CONARIUM**

Pineal body.

**CONDYLE**

End of a bone fitting into a socket.

**CONHYDRINE**

$C_8H_{17}ON$ ; 2-alpha-hydroxy-propylpiperidine; odorous, basic alkaloid of hemlock; colorless leaflets, m.p. 121°; poisonous, causing paralysis of the motor nerve endings, respiratory paralysis, and death.

**ψ-CONHYDRINE**

$C_8H_{17}ON$ ; 5-hydroxy-2-propylpyridine; an alkaloid of hemlock; needles from ether, m.p. 105-6°; poisonous, causing paralysis of the motor nerve endings, respiratory paralysis, and death.

**CONICEINES**

A group of 6 basic amines, prepared from hemlock alkaloids. They are pyridine or piperidine derivatives.

**CONIFERIN**

$C_{18}H_{22}O_8$ ; a glycoside of the bark of the fir tree, consisting of glucose and coniferyl alcohol; it crystallizes as needles, m.p. 185°C.

**CONIFERYL ALCOHOL TEST**

See Reinitzer.

**CONIINE**

$C_8H_{17}N$ ; alpha-propyl-piperidine; a colorless, odorous, alkaline alkaloid of hemlock; oil, b.p. 166-7°, poisonous, causing paralysis of the motor nerve endings, resulting in respiratory paralysis and death.

**CONIINE TEST**

See Reichard.

**CONJUGATION**

Fusion of two cells accompanied by pooling or exchange of nuclear materials and chromatin, temporarily or permanently, the cells being one male and the other female, the purpose in some cases being a rejuvenation where the sex difference may be doubted.

See Detoxication.

## CONJUNCTIVA

The mucous lining of the eyelids.  
See Eye, Biochemistry of.

## CONJUNCTIVITIS

Inflammation of the conjunctiva of the eye which may be (1) simple or catarrhal, characterized by infection or associated with skin diseases, catarrhs, measles, smallpox, scarlet fever, trauma; (2) acute contagious or "pink eye" or Koch-Weeks conjunctivitis or epidemic conjunctival catarrh, caused by the Koch-Weeks bacillus; (3) *Diplobacillus conjunctivitis*; (4) conjunctivitis neonatorum or ophthalmia neonatorum due to infection usually by gonococcus; (5) adult gonococcal conjunctivitis; (6) pneumococcal conjunctivitis; (7) scrofulous ophthalmia or eczema of conjunctiva, occurring in tubercular cases; (8) trachomatous or granular conjunctivitis or trachoma or Egyptian ophthalmia, which is very contagious; (9) vernal or spring conjunctivitis characterized by flat granulations; and (10) and many others, e.g. allergic, diphtheritic, traumatic.

Aside from causal treatment, cod-liver oil, iron, arsenic are administered. Atropine is used in cases of excessive irritation. Usual drugs for direct application are silver nitrate, boric acid, zinc sulfate, tannic acid, silver proteinate, ichthyol.

## CONNECTIVE TISSUE

A loose tissue found in and supporting the various organs, consisting of about 60% water, 32% collagen, 0.5% inorganic matter, and the remainder largely lipids.

## CONQUININE

See Quinidine.

## CONTRACTILE VACUOLE

A primitive organ of excretion in the cytoplasm of single-celled organisms, consisting of a liquid-filled cavity which shows periodic contraction.

## CONVALLATOXIN

A glucoside; the most toxic of the known heart glucosides according to tests on frogs.  
See Digitalis.

## CONVOLVULIN

A glycoside of jalap root, yielding on hydrolysis 4 mols. glucose, 2 mols. rhamnose and convolvulinic acid or 3:12-dihydroxyhexadecanoic acid; used as purgative.

## COPAIBA

An oleo-resin of *Copaifera* which on account of its antiseptic powers has been used in the treatment of gonorrhea.

## COPEPODS

Water-fleas.

## CO-PIGMENTS

See Genetics, Biochemical.

## COPPER TESTS

See Callan-Henderson.

## COPROPHAGY

Feeding on excrement.

## COPROPORPHYRIN

$C_{36}H_{36}O_8N_4$ ; a porphyrin present in urine and feces and in larger amounts in certain pathological conditions including pernicious anemia and hemolytic jaundice; an isomer is excreted in lead poisoning and forms of liver degeneration.

## COPROSTEROL

$C_{27}H_{48}O$ , m.p.  $102^\circ$ ; a saturated sterol found in feces. H. S.

## CORAMINE

Pyridine- $\beta$ -carboxylic acid diethylamide; yellow liquid; used in cardiovascular collapse, bronchial

asthma as a respiratory stimulant instead of camphor; dose, 1-2 cc. of a 25% solution orally, subcutaneously or intravenously.  
See Pharmacology.

### CORBASIL

$\beta$ -hydroxy- $\beta^1$ -(3, 4-dihydroxy-phenyl)-isopropylamine; a preparation related to ephedrine and epinephrine.

### CORDATE

Heart shaped.

### CORIANDER

Dried fruits of *Coriandrum sativum*, used as a carminative.

### CORI ESTER

Alpha glucopyranose-phosphoric acid.

### CORIUM

Cutis; skin layer below epidermis.

### CORNEA

See Eye, Biochemistry of.

### CORPORA AMYLACEA

Brain sand.

### CORPORA STRIATA

A pair of brain ganglia serving as pathways for nervous impulses between higher and lower centers.

### CORPORIN

See Progesterone.

### CORPUS CALLOSUM

Bands of nerve fibres bridging both halves of the mammalian brain.

### CORPUS LUTEUM

The second stage of the development of the mammalian Graafian follicle of the ovary after it has ruptured and discharged an ovum. It secretes the hormone progesterone which is of prime importance in the regulation of pregnancy and its sequellae.

### CORPUS LUTEUM HORMONE

See Progesterone.

### CORTALEX

A commercial preparation of natural adrenal cortex hormone extract.

### CORTATE

A commercial preparation of synthetic desoxycorticosterone acetate.

### CORTEX

Rind; gray matter (brain); outer protective part of an organ or gland such as the kidney, adrenals, etc.

### CORTICOSTERONE

An active constituent of cortin, the natural hormone of the adrenal cortex; it is  $C_{21}H_{30}O_4$  or  $\Delta^4$ -pregnene-11,21-diol-3,20-dione; measured by its ability to counteract fatigue of adrenalectomized rats, and other effects of adrenalectomy.

### CORTICOTROPIN

A hormone of the anterior pituitary, to which has been ascribed the power of controlling the adrenal cortex secretion.

### CORTILACTIN

A hormone of the adrenal cortex, which apparently has some effect on the mammary glands; its nature is not known.

### CORTIN

The hormone or hormone mixture of the adrenal cortex, the absence of which is fatal. To a large extent it controls the physical and mental sexual character. It also controls the Na/K ratio of the blood, and probably a number of other functions.

**CORTIPRESSIN**

A hormone of the adrenal cortex which causes a rise in blood pressure; its chemical nature is not known.

**CORYBULBINE**

$C_{21}H_{25}O_4N$ ; colorless needles, m.p.  $238^\circ$ ; alkaloid of *Corydalis*; causes drop in blood pressure in mammals.

**CORYCAREDINE**

$C_{22}H_{25}O_5N$ ; crystallizes with 1  $CHCl_3$ , m.p.  $212-213^\circ$ , alkaloid of *Corydalis* root.

**CORYCAVAMINE**

$C_{21}H_{21}O_5N$ ; rhombic columns, m.p.  $149^\circ$ ; alkaloid of *Corydalis* root; stereoisomeric with corycavine, and has a similar physiological activity.

**CORYCAVINE**

$C_{21}H_{21}O_5N$ ; rhombic tablets, m.p.  $217-218^\circ$ ; alkaloid of *Corydalis* roots stereoisomeric with corycavamine; in frogs causes narcosis and spinal cord paralysis; in mammals stimulates tear and saliva flow and causes epileptiform convulsions; also interferes with the heart action.

**CORYNINE**

See Yohimbine.

**COTARNINE**

$C_{12}H_{15}O_4N$ , oxidized narcotine; used medicinally to check hemorrhage; trade name "stypticin" and as phthalate "styptol"; also used as ointment for shingles, eczema, etc.

**COTTRELL PRECIPITATION**

The precipitation of colloids by passing the colloid past oppositely charged plates; also called electrical precipitation, especially for dispersions of solids in gases.

**COTYLEDON**

- (1) primary seed leaf of seedling tree or flowering plant.
- (2) group of villi on placenta of mammals.

**COUMARIN**

The flavor substance of the Tonka bean; odorless; the anhydride of coumaric acid made from salicyl aldehyde by closure with acetic anhydride;  $C_9H_6O_2$ , m.p.  $70^\circ$ .

**COUMARINE GLYCOSIDES**

Compounds of glucose with derived coumarins, found in many plants, e.g. aesculin, daphnin, fabiatriin, fraxin and scopolin.

**COUPLING OF OXIDATION PROCESSES**

The biological coupling of processes which enable a process requiring much energy to take place, e.g. aerobic oxidations with the production of urea in the ornithine cycle which requires energy from an outside source.

**COZYMASE (Coenzyme I)**

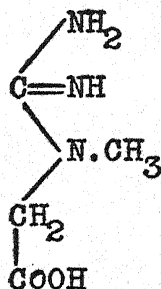
A co-enzyme of apozymase, without which zymase preparations do not have the power to ferment. It is a mononucleotide of molecular weight about 350, containing nicotinic acid amide, pentose, adenine and phosphoric acid. It probably combines with a specific protein of zymase to become an active enzyme.

**CREATINE AND CREATININE METABOLISM**

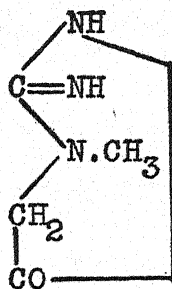
1. Definitions. Creatine is methyl guanidine acetic acid and creati-



nine is its anhydride, or methyl glycoamidine.



**Creatine**



**Creatinine**

Total Creatinine is the total amount of creatine and creatinine present in body tissues and fluids.

Preformed Creatinine is the difference between the total creatinine and creatine in body tissues and fluids, or if no creatine is present, the amount of creatinine, i.e., in the urine.

Creatine "As Creatinine" is the difference between the total and preformed creatinine in the urine.

Creatine is the difference between the total and preformed creatinine in the urine  $\times 1.16$ .

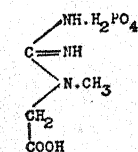
"Apparent" Creatine and Creatinine is the respective amounts of chromogenic material in body tissues and fluids which are given by the Jaffé reaction with alkaline picrate. (This is the usual meaning of the terms creatine and creatinine expressed in the literature).

"True" Creatine and Creatinine is that amount of the Jaffé reaction with alkaline picrate which is destroyed by the specific creatinine enzyme of Miller and Dubos<sup>1</sup> (i.e., 80 per cent of the chromogenic color may be due to true creatine

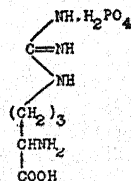
or creatinine and 20 per cent to some other substance, such as glycoamidine, hydantoin, acetoacetic acid, etc. The specific creatinine enzyme will destroy the 80 per cent of true creatine or creatinine but not the other 20 per cent).

"Residual" Creatine and Creatinine is that part, (i.e., the 20 per cent referred to above) of the Jaffé reaction with alkaline picrate which is not destroyed by the specific creatinine enzyme of Miller and Dubos.

Creatine Phosphate occurs in mammalian and heart muscle and in nerve tissue. Arginine phosphate occurs in invertebrate muscle.



**Creatine Phosphate**



**Arginine Phosphate**

Creatinemia is an increase in the creatine content of the blood above 3 mg. per 100 cc.

Creatininemia is an increase in the creatinine content of the blood above 1.5 mg. per 100 cc.

Creatinuria is the presence of extra creatine in the urine per day.

Creatininuria is the presence of extra creatinine in the urine per day.

Creatine Tolerance is the amount of creatine retained by the tissues after ingesting 1.32 gms. of creatine.

Creatinine Clearance is the number of cc. of plasma cleared of creatinine per minute after ingestion of 5 gms. of creatinine.

Creatinine Coefficient is the mg. of creatinine excreted per day per kilo body weight.

2. Distribution. Creatine occurs in the muscles, heart and nerve tissues of various species of animal and man. It is the chief nitrogenous constituent of muscle and its concentration will average about 0.4 per cent. About three-fourths of the creatine in muscle tissue and one-half in heart muscle is present as creatine phosphate. The creatine concentration in the blood will average about 2.5 mg./100 cc.

Creatinine occurs only in traces in the tissues. Its excretion in the urine of different individuals may vary from 0.8 to 2.5 gms. About 1.5 gm. are excreted daily in normal adult urine. Its excretion is not necessarily constant but uniform, from day to day, and is dependent upon the rate of protein metabolism rather than upon the body weight of the individual. The creatinine concentration in the blood is about 1 mg./100 cc.

Baker and Miller<sup>2</sup> showed that true creatinine comprises from 80 to 100 per cent of the chromogenic material of serum and plasma and from 30 to 50 per cent in the red cells. In the urines from normal and nephritic individuals, true creatinine constituted nearly 100 per cent of the chromogenic material. Most of the chromogenic material of muscle filtrates is true creatine. In skeletal and heart muscle, testes and brain of the rat, the true creatine averages from 83 to 96 per cent of the apparent creatine, while, in intestinal muscle, pancreas, spleen, lung and liver the true creatine amounts to only 16 to 65 per cent of the apparent creatine.

3. Methods Used. Several methods have been proposed for determination of creatinine. Only one, however, has been used consistently in the past. This is the adaptation of the Jaffé reaction with alkaline picrate introduced by Professor Polin in 1905.<sup>3</sup> This is considered as the standard method for the determination of creatinine at the present time.

Preformed Creatinine in Urine. To a small amount of the 24-hour urine specimen (1 cc.) in a 100 cc. volumetric flask 10 cc. purified picric acid and 1.5 cc. of 10 per cent NaOH are added. At the end of 10 minutes after shaking the flask the sample is diluted to the mark and compared with 1 mg. of creatinine prepared in a similar flask as a standard. A visual colorimeter or a photoelectric colorimeter may be used in matching the colors. The latter type of instrument is becoming more and more popular at the present time.

Total Creatinine in Urine. To a similar amount of the 24-hour specimen, say 1 cc. in a 100 cc. volumetric flask, add 1 cc. of (1 to 4) HCl, cover the flask with a small beaker or crucible and autoclave at 15 lbs. pressure for 30 minutes. (Under acid hydrolysis creatine is dehydrated to creatinine). Cool, neutralize, add alkaline picrate, dilute to the mark and complete the color matching as described above for preformed creatinine.

Creatine "As Creatinine" in Urine.

Total creatine minus preformed creatinine equals creatine "as creatinine."

Creatine, as creatinine,  $\times 1.16 =$  creatine.

Total Creatinine in Tissues. Since

only small traces of creatinine are present in the tissues, the total creatinine is determined and taken to represent the creatine content. The method of Rose, Helmer and Chanutin<sup>4</sup> gives excellent results. In this method a sample of about 1 gm. of tissue is removed from the animal within 10 minutes after death, cut up fine with scissors, weighed into a 50-cc. glass stoppered Erlenmeyer flask and placed under 20 cc. of 2 N sulfuric acid and autoclaved for 45 minutes at 15 lbs. pressure. After cooling, the contents of the flask are poured into a 100 cc. volumetric flask with the aid of about 25 cc. of distilled water; 18 cc. of 2 N NaOH are then added, followed by 5 cc. of 10 per cent sodium tungstate, and the whole finally made up to the mark. The flask is shaken and after 5 minutes the contents are filtered. Ten cc. of the clear filtrate are used for the determination of total creatinine with alkaline picrate and compared with the standard as described above. The Fisher electro-photometer can be used for matching the colors.<sup>6</sup>

In muscle filtrates and urine practically all of the chromogenic color with alkaline picrate is true creatine and creatinine. For routine determinations the above methods may be used. In the analysis of creatine and creatinine in other tissues, however, the use of the specific creatinine enzyme method of Miller and Dubos<sup>1</sup> must be used to get the true creatine content. In this method the "apparent creatinine" is determined as above. Then the same amount of urine, or tissue filtrate, is incubated at 37°C with the bacterial enzyme in a phosphate buffer of pH7. In about 1 hour the solution is filtered into a 100 cc. volu-

metric flask, alkaline picrate is added and the determination completed as usual. If no color develops, 100 per cent of the original color was due to "true creatinine." In many cases some color may be left which is not destroyed by the enzyme. Hence the "apparent creatinine" (or Total Creatinine)—the "residual creatinine"—"true creatinine." It is to be remembered here that most of the published values for creatine and creatinine in the literature for body tissues and fluids represented the "apparent" creatine and creatinine. Since it is very difficult to cultivate the bacterial enzymes of Miller and Dubos it is possible that, for routine purposes, these substances will continue to be determined as usual and be simply called creatine and creatinine.

**Creatine and Creatinine in Blood.** The tungstic acid blood filtrate is treated with the alkaline picrate solution and these substances determined as outlined above. (Cf.<sup>5</sup>). The determination of blood creatine has little diagnostic significance. The determination of the creatinine content is sometimes useful in diagnosis, especially in diseases of the kidney and in other cases of nitrogen retention. A value of 2 mg./100 cc. is abnormal and one of 5 mg./100 cc. or above is usually of grave prognostic significance (Andes and Eaton<sup>5</sup>). A value of 3 mg./100 cc. usually indicates marked functional deficiency in the kidneys as determined by the urea clearance test. Values from 20 to 35 mg./100 cc. have been observed in terminal nephritis. In bichloride poisoning and after nephrectomy a progressive rise in blood creatinine occurs due to the anuria present.

**Creatinine Clearance.** A given

amount of creatinine is ingested and the rate of its excretion is determined by comparing the concentrations of creatinine simultaneously in urine and plasma. This test of kidney function is losing much of its physiological importance at the present time.<sup>8</sup>

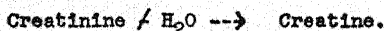
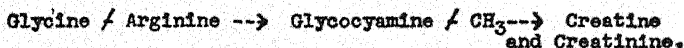
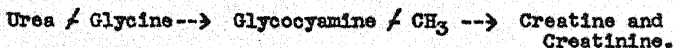
**Creatine Tolerance.** This is a test to determine the ability of the muscles to store creatine after its ingestion. It has been used largely in diseases of the muscles, such as in the dystrophies and atrophies. A sample containing 1.32 gm. of creatine is ingested by the patient and the amount of creatine excreted in the urine is determined. The amount of creatine excreted usually depends upon the amount ingested, which is not more than 1 or 2 per cent of the total amount of creatine in the tissues. From 20 to 100 per cent of this creatine may be excre-

ted or retained. At the present time the test seems to have little physiological or diagnostic significance.<sup>9</sup>

**4. Findings, Correlations, Generalizations.** In the past it was generally believed that both creatine and creatinine were products of the endogenous metabolism and that diet had no effect on their concentration in body tissues and fluids. Recent evidence shows that no distinction is to be drawn between the exogenous and endogenous metabolism.<sup>6,7</sup> Experimental data obtained from 1925 until the present time have, therefore, considerably change our conceptions of creatine and creatinine metabolism.

#### Origin of Creatine and Creatinine.

At the present time there are three main pathways by which these substances are formed in vitro and in vivo. These are as follows:



Glycocyamine is the most important precursor of creatine and creatinine and is widely distributed in the tissues (Borsook and Dubnoff<sup>8</sup>) and it also occurs normally in the urine (Weber<sup>9</sup>). It is formed in various tissues, such as the muscles, liver and kidneys, from any of the amino acids of the diet, except proline and hydroxyproline. The amino group of the amino acid is necessary for creatine and creatinine formation.<sup>6</sup>

While the above reactions are the principal ones for the formation of creatine and creatinine in the body, these reactions may also

occur after administration of about 50 different substances.<sup>6</sup> Several amino acids and their methylated derivatives, methionine, methyl methionine, glycine, methyl glycine (sarcosine), glycollic acid, formaldehyde, and the methyl group of the purines, as well as those of choline, betaine, etc., can be utilized for the methylation of glycocyamine to creatine. The "transmethylation" of the methyl group from these compounds to glycocyamine is believed to occur in the liver. The methyl group must be transferred as a unit. A lack of available methyl groups in the diet will result in pathological lesions in the kidneys

which can be cured or prevented by supplying methyl groups, such as occur in choline, in the diet.

**Creatine-Creatinine Retention and Excretion.** When these substances are ingested from 20 to 100 per cent may be either retained or excreted, depending on the individual.<sup>6</sup> This is an excellent example of the variations one encounters in this type of research. Both creatine and creatinine can be oxidized in the tissues into other substances (see next section). A little creatine may be excreted in normal individuals, while the creatinine excretion is usually considered to be fairly uniform in a given individual, but it may vary as much as 100 per cent in different individuals. In health, the excretion of extra creatine and creatinine into the urine represents those amounts formed and not stored or oxidized in the tissues.

These results help one to visualize the extent of creatine and creatinine retention and excretion. Bloch and Schoenheimer<sup>10</sup> do not believe that creatine is changed into other substances except creatinine, in the tissues. They stated that

Creatinine / tissues (creatinine oxidase) → oxidation products

Creatinine / tissues (creatinine hydase) → creatine

Creatine / tissues (creatine oxidase) → oxidation products

Creatine anhydase, for the conversion of creatine to creatinine, did not occur.

In the rat and man administration of creatinine also greatly stimulates the excretion of both creatine and creatinine.<sup>6</sup> It seems, therefore, that there is no biological relation between administered creatin and creatinine, but there is a definite biological relation between administered creatinine and creatine. No

about 2 per cent of the newly formed creatine was excreted daily as creatinine, but this calculation stands in need of revision since Bodansky et al.<sup>11</sup> showed that creatine was also excreted by way of the intestine even in cases of starvation preceded by a period of feeding a creatine-free diet. On the other hand, creatine was not changed into creatinine in any of the studies of Beard et al.,<sup>6</sup> and, even though it is well known that the methyl group of creatine and creatinine is stable in the body, nevertheless our evidence shows that these substances may still be oxidized in the tissues, probably into methyl guanidine and oxalic acid.

**Biological Relation between Administered Creatine and Creatinine.** Before 1925 it was generally believed that creatine was dehydrated into creatinine which was then excreted into the urine. This change has, however, never occurred in at least 10 of our studies<sup>6</sup>. All of our evidence is for the reverse transformation. When we incubated creatine or creatinine with different rat tissues the following reactions occurred:

conclusion can be drawn for the biological relation of body creatine and creatinine since there is no method to study this relation at the present time. Evidence was also obtained to show that the body metabolizes administered creatine and creatinine in a different manner from the way it does when these

substances arise normally during protein Catabolism in the body (Cf. next section).

**Creatine-Creatinine Metabolism in Relation to Water Metabolism.** In line with the above results creatinine, injected with water or saline, increases creatine excretion. Under similar conditions creatine again did not form creatinine. The posterior pituitary hormones, pitressin and pitocin, caused a retention of body creatinine which was quantitatively transformed into body creatine and excreted as such, while these hormones had no influence upon administered creatinine under these conditions.<sup>6</sup>

**Creatine-Creatinine and Endogenous and Basal Metabolism.** No relation exists between the endogenous and basal metabolism and creatine-creatinine metabolism.<sup>6</sup>

**Creatine-Creatinine Metabolism and the Hormones.** For obvious reasons this relation is difficult to study. The extensive literature and results of the studies of the author have been reviewed.<sup>6</sup> The effect of several of these hormones on the creatinine-creatine transformation was stated to be due to water and salt retention. This transformation also depends upon the presence of the gonads.

**Creatine-Creatinine Metabolism and the Vitamins.** Choline definitely increases the methylation of glycocyamine to creatine. None of the other vitamins studied, except niacin,  $\alpha$ -tocopherol and pyrodoxin, affects this type of metabolism.<sup>6</sup>

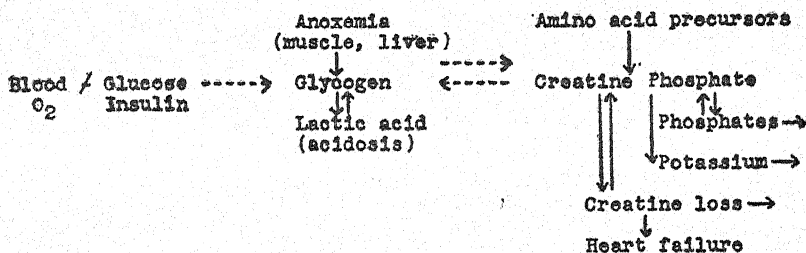
**Nutritional Muscular Dystrophy.** This syndrome may be produced in rabbits, guinea pigs and other animals by feeding them on diets lacking vitamin E. It also occurs in

the young of mothers fed on just enough vitamin E to permit reproduction. The creatine and phosphate concentration of the muscles is below normal. Addition of vitamin E prevents and cures the condition and raises the creatine and phosphate content of the muscles back to normal. Some types of amyotrophic lateral sclerosis in man, but not all, respond to vitamin E administration.<sup>6</sup>

**Human Myopathies and Creatine Metabolism.** In many of these diseases of the muscles there is a lowered creatine content accompanied, usually but not always, by creatinuria. This creatinuria increases for a few weeks after the amino acids glycine, glutamic acid, etc., are ingested and then returns to its former level. During this time some cases improve clinically but there are many that do not. Best results are obtained in the dystrophies as compared to the atrophies. Glycine therapy should be continued throughout the life of the patient and the degeneration of the muscle tissue should not have reached a point where regeneration is impossible.

**Significance of the Creatine Content of the Heart.** Creatine is also present in the heart in the form of creatine phosphate and functions here as it does in the muscles, i.e., helps in increasing the contractions of the heart. In many cases of cardiac failure there is a lowered creatine and phosphate content of the heart and this is the cause of the disease (Hermann<sup>19</sup>).





Administration of glycine has proved of much benefit to patients suffering from heart disease as well as many different types of diseases of the eye.

The Relation between Creatine and Carbohydrate Metabolism; Creatinuria. The oxidation of carbohydrate in the tissues is closely

associated with phosphate, lactate and creatine metabolism. (Cf. M. R. Everett, Medical Biochemistry, Paul B. Hoeber, Inc., 1942, p. 298).

Chemistry of Muscular Contraction and Recovery. The modern conception of muscular contraction<sup>13,14</sup> is as follows:

- (1) Adenyl-pyrophosphate  $\longleftrightarrow$  Adenylic acid /  $H_3PO_4$   
(Energy for contraction)
- (2) Creatine Phosphate  $\longleftrightarrow$  Creatine /  $H_3PO_4$   
(Energy for the resynthesis of adenylpyrophosphate)
- (3) Glycogen to lactic acid.  
(Energy for the resynthesis of creatine phosphate)
- (4) Oxidation of 1/5 of the lactic acid.  
(Energy for the resynthesis of the remainder of the lactic acid to glycogen)

The enzyme adenylpyrophosphatase, which catalyzes reaction 1 above, has been shown to be identical with the muscle protein myosin (Cf.<sup>8</sup>).

Creatinuria occurs in many diseases, i.e., of the muscles and liver, and in fever, diabetes, hyperthyroidism, etc. Creatinuria, per se, therefore, does not represent creatine liberated from the muscle tissue and it cannot be used alone as a diagnostic test for diseases of the muscles. Physiological creatinuria, which may occur in the urine of

men, women and children, on the other hand is known to be due to an increased formation and excretion of creatine from its precursors in the diet. The muscles can store from 50 to 100 per cent creatine above normal for a short time only.

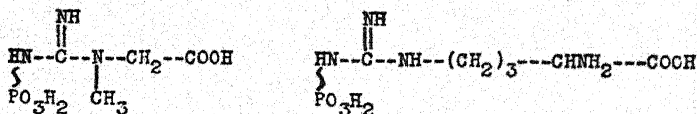
The creatinuria of carbohydrate deprivation is abolished by feeding sugar. There are at least three theories to account for the excretion of creatine in the urine. First, that of Brentano<sup>15</sup> which states that creatinuria is due to a breakdown of glycogen or to a defective utiliza-

tion of carbohydrate; Wang,<sup>27</sup> second, that of Myers and Fine<sup>16</sup> which states that it is due to a disintegration of muscle tissue with resulting liberation of muscle creatine which is then excreted into the urine; and third, that of Beard which states that it is due to a lack of phosphate donators in the tissues to hold the creatine as creatine phosphate.<sup>6</sup>

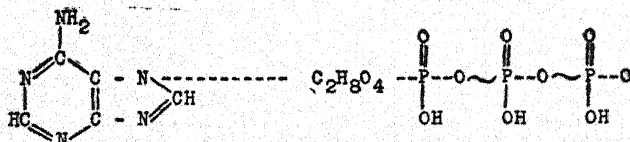
**Muscular Exercise, Creatine-Creatinine Metabolism and the Effect of Ingestion of Amino Acids upon Energy Output.** Protein, fat and carbohydrate can all, either directly or indirectly, furnish the fuel for muscular work. The creatine-creatinine excretion is usually not affected in muscular exercise. Since the amino acid glycine has been ingested to improve the nutritive condition of many individuals suffering from various diseases of the muscles and heart, it was to be expected that it would be utilized to increase energy output and resistance to fatigue in normal individuals. Several investigators have secured negative results on increasing energy output using glycine or gelatin.

Increases energy output in males (Ray et al.<sup>17</sup>) and males and females (Kaczmarek.<sup>18</sup> Glycine does likewise (Chaikelis<sup>19</sup>) and glycine and urea give about twice the increased energy output as compared to glycine alone.<sup>6</sup> The increased energy output is also directly proportional to the amount of glycine ingested. It takes about 3 weeks for improvement to be noticed, and this lasts as long as the glycine is ingested. When it is discontinued the energy output drops in 3 days to the normal control level which nature has bestowed on each individual. Increases in energy output from 60 to 100 per cent above normal have been observed with glycine in 75 per cent of our students. The addition of vitamin B<sub>1</sub> is also beneficial with glycine. Confirmation of these findings is shown in the extensive use of this amino acid for increasing the energy output. Administration of creatinine, with and without phosphate, also increases energy output, while creatine, under similar conditions, does not do so.<sup>6</sup>

**Phosphate Bond Energy.** The phosphate bond energy in creatine and arginine phosphates is located as follows: (Lipmann<sup>20</sup>):



In adenosine triphosphate these energy rich bonds are located between the oxygen and phosphorus, as follows:



In these compounds the energy rich bonds are designated between N and P and O and P by the symbol ~

According to Lipmann, reaction phases can be determined in the constantly occurring metabolic turnover of phosphate. These are: (1) introduction of inorganic phosphate into ester linkage; (2) the generation of energy rich bonds ( $\sim$  ph) by oxidation-reduction reactions; (3) the taking over and distribution of ( $\sim$  ph) and the regeneration of inorganic phosphate. For the maintenance of these complicated reactions there must be a well balanced equilibrium between the great number of enzymatic reactions involved. Removal of the energy rich phosphate bond in oxidation-reduction reactions by adenylic acid occurs. A fine interplay between oxidation-reduction and phosphorylation-dephosphorylation results. It is, therefore, seen that phosphate enters into primary organic bonds over the pathway of oxidation-reduction reactions. Under these conditions phosphate bonds of high potential are formed by "transphosphorylation" and in the cells this high potential is maintained, or a fall in potential occurs with the formation of an ester bond. The phosphate bond energy ( $\sim$  ph) generated in the oxidation-reduction is removed from phosphoglyceric acid with the conservation of the bond energy through adenylic acid. It finally appears in the muscle as creatine phosphate bond energy. This is then drawn from the anaerobic cycle as phosphate bond energy. Lipmann is of the opinion that no decision at present can be offered as to where the phosphate bond energy is taken off to operate contraction. It is possible that muscular contraction is operated by energy derived from both aerobic and anaerobic bond energies.

#### The Oxidation-Reduction Reaction.

When glucose is split into 2 lactic acids, 4 phosphate bond energies are made available by the formation of 2 bond energies in the oxidation-reduction reaction and 2 enol-phosphates by dehydration of phosphoglyceric acid. If glycogen is the substrate, 3 and possibly 4 of the phosphate bond energies remain available. For every mole of glycogen-glucose metabolized, 4 moles of creatine phosphate can be reformed in the recovery phase of muscular activity. With glucose, however, where 2 of the phosphate bond energies are used for primary phosphorylation, only 2 of the 4 phosphate bond energies remain available. The change in free energy with the decomposition of an energy-rich phosphate bond amounts to  $-10,000$  cal. The  $40,000$  cal., represented by the 4 phosphate rich bonds, can then be compared to the total change in free energy with the decomposition of 1 mole of glucose (glycogen) to 2 moles of lactic acid. For this reaction Burk calculated  $\Delta F = \text{ca. } -58,000$  cal. Hence up to 70 per cent of the total energy may be converted into phosphate bond energy.

**Phosphorylation and Respiration.** Lennerstrand and Runnström<sup>21</sup> observed a coupling between phosphorylation and respiration in dry yeast preparations. Lipmann<sup>20</sup> showed that the dehydrogenation of pyruvate by *Bacterium Delbrueckii* was a non-fermentable reaction and that it was coupled with phosphorylation. Phosphorylations coupled with respirations have also been observed in animal tissues. The coupled phosphorylation system requires  $\text{Mg}^{++}$ , succinic acid and pyridine nucleotide (cozymase). For every mole of glucose oxidized to  $\text{CO}_2$  an additional 5 or 6 moles of

glucose disappear, 5 moles of which are accumulated as fructose-di-phosphate. Probably 10, if not 12, steps in glucose combustion can give rise to phosphate uptake.

There is a marked stimulation of the respiration of muscle pulp by creatine, during which time creatine is phosphorylated to creatine phosphate, Belitzer.<sup>22</sup> The increase in respiration by creatine is determined by its capacity to accept phosphate groups. This is the first demonstration of the coupling between phosphorylation and respiration in animal tissues. In the words of Szent-Györgyi,<sup>23</sup> "Whatever the mechanism of the energy transfer of the electron transport may be, the importance of the phosphoric acid esters, in the problem of biological research which, I expect, doubt. The discovery of this energetic significance of phosphate is one of the most important and striking discoveries of modern biological energetics, admits of little will, in the future, open unforeseen vistas, and will bring us closer to an understanding of life."

**Amino Acid, Creatine and Cancer Metabolism.** Creatine is formed from the amino acids in metabolism and these substances also cause large numbers of experimental tumors in rats to disappear.<sup>6</sup> In those that do not disappear the rate of growth is only one-third that of the control tumors. Both guanidine derivatives (guanidine, glycocyamine, creatine, creatinine, etc.) and other amino acids and nitrogenous and purine bases and amines from muscle, cause tumors to disappear (Lustig and Wachtel,<sup>24</sup> Roffo,<sup>25</sup> Beard,<sup>6</sup> Boyland.<sup>26</sup>

**5. Problems and Research Trends.** Some important problems in crea-

tine and creatinine metabolism would be the following: The relation of creatine and phosphate metabolism; the methylation of glycocyamine to creatine; the methylation of glycocyamine to creatinine; the addition of an NH group to hydantoin and hydantoic acid with the formation of glycocyamine and glycocyamine, respectively; the precursors of urea in relation to creatine formation; injection of creatinine with methylating agents on creatine formation; the preparation of creatinine phosphate and the influence of its administration on the formation of creatine phosphate in the muscles; the production of nutritional edema and its relation to muscle creatine; a study of creatine excretion in uremia and in diabetes insipidus; the effect of sugars upon creatine excretion; the origin of glycine; the nature of creatine and creatinine metabolism using the N isotope and radiophosphorus; functions of creatine in carbohydrate metabolism (oxidation-reductions, phosphorylations-dephosphorylations, energy transfer, etc.); the source of the increased creatine content of the muscles in starvation; the effect of meat feeding upon creatine and creatinine metabolism; the nature of the oxidation products formed from creatine and creatinine by the Miller and Dubos specific creatinine enzyme; discovery of other bacterial species that destroy creatine and creatinine; relation of amino acid, creatine and cancer metabolism.

**Research Trends.** The relation of creatine to (a) phosphorylation and respiration, (b) phosphate bond energy, (c) mechanism of energy transport in the cell, (d) to sugar metabolism, (e) to phosphorus metabolism, f) to muscular contraction (including relation of myosin

to adenyl pyrophosphatase), (g) to the blood sugar level, (h) to nutritional muscular dystrophies and atrophies, (i) to creatinine, water and salt metabolism, (j) to diseases of the heart and muscles in man, and (k) to amino acid and cancer metabolism.

See also Myocardium, Biochemistry of.

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#### SELECTED REFERENCES

- <sup>1</sup> Miller, B. F. and Dubos, R., *J. Biol. Chem.*, 121: 429, 1937; 121: 447, 1937; 121: 457, 1937; 130: 383, 1939.
- <sup>2</sup> Baker, Z. and Miller, B. F., *J. Biol. Chem.*, 130: 393, 1939.
- <sup>3</sup> Folin, O., *Am. J. Physiol.*, 13: 45, 1905; 13: 66, 1905; 13: 117, 1905; *J. Biol. Chem.*, 17: 469, 1914; 17: 475, 1914; 17: 493, 1914.
- <sup>4</sup> Rose, W. C., Helmer, O. M. and Chanutin, A., *J. Biol. Chem.*, 75: 543, 1927.
- <sup>5</sup> Andes, J. E. and Eaton, A. G., *Synopsis of Applied Pathological Chemistry*, p. 83, C. V. Mosby Co., St. Louis, 1941.
- <sup>6</sup> Beard, H. H., *Creatine and Creatinine Metabolism*, Chemical Publishing Co., Brooklyn, N. Y., 1942.
- <sup>7</sup> Schoenheimer, R., Ratner, S. and Rittenberg, D., *J. Biol. Chem.*, 130: 703, 1939.
- <sup>8</sup> Borsook, H. and Dubnoff, J. W., *J. Biol. Chem.*, 132: 559, 1940; 134: 627, 1940; 138: 389, 1941.
- <sup>9</sup> Weber, C. J., *J. Biol. Chem.*, 96: 217, 1930; 88: 353, 1930.
- <sup>10</sup> Bloch, K. and Schoenheimer, R., *J. Biol. Chem.*, 131: 111, 1939.
- <sup>11</sup> Bodansky, M., Duff, V. D. and McKinney, M. G., *J. Biol. Chem.*, 140: 365, 1941.
- <sup>12</sup> Hermann, G., *Synopsis of Diseases of the Heart and Arteries*, p. 231, C. V. Mosby Co., St. Louis, Mo.
- <sup>13</sup> Meyerhof, O. and Lohmann, K., *Biochem. Z.*, 255: 431, 1932.
- <sup>14</sup> Lohmann, K., *Biochem. Z.*, 271: 264, 1934.

<sup>15</sup> Brentano, C., *Arch. exp. Path. Pharm.*, 155: 21, 1930; 157: 125, 1930; 163: 156, 1931; *Deutsch. med. Wochenschr.*, 58: 699, 1932; 59: 448, 1933.

<sup>16</sup> Myers, V. C. and Fine, M. S., *J. Biol. Chem.*, 15: 283, 1913; 14: 9, 1913; 21, 533, 1915.

<sup>17</sup> Ray, G. B., Johnson, J. R. and Taylor, M. M., *Proc. Soc. Exp. Biol. and Med.*, 40: 157, 1939.

<sup>18</sup> Kaczmarek, R. M., *Res. Quart.*, 11: 283, 1940; *Med. Rec.*, June 4, 1941, p. 428; June 18, 1941, p. 428.

<sup>19</sup> Chaikalis, A. S., *Am. J. Physiol.*, 132: 578, 1941.

<sup>20</sup> Lipmann, F., *Advances in Enzymology*, Interscience Publishers, Inc., New York, 1941, p. 99.

<sup>21</sup> Lennerstrand, A. and Runnström, J., *Biochem. Z.*, 283: 12, 1935.

<sup>22</sup> Belitzer, V. A., *Biokhimiya*, 4: 616, 1939; 4: 498, 1939; 2: 332, 1937; 3: 80, 1938.

<sup>23</sup> Szent-Györgyi, A. v., *Oxidations, Fermentations, Vitamins, Health and Disease*, William and Wilkins Co., Baltimore, Md., 1939.

<sup>24</sup> Lustig, B. and Wachtel, H., *Z. Krebsforsch.* 43: 54, 1935; *Bull. Assn. franç. p. l'étude du Cancer*, 25: 542, 1936.

<sup>25</sup> Roffo, A. H., *Bol. Instit. de Med. Exp. para el estud. y trat. del Cancer*, Ano. No. 45: 257, 1937.

<sup>26</sup> Boyland, E., *Biochem. J.*, 35: 1283, 1941.

<sup>27</sup> Wang, E., *Clinical and Experimental Investigations on the Creatine Metabolism*, Mercators Tryckeri, Helsingfors, 1939.

#### MONOGRAPHS AND REVIEWS

<sup>1</sup> Hunter, A., *Creatine and Creatinine*, Longmans, Green & Co., New York, 1928.

<sup>2</sup> Myers, V. C., *Yale J. Biol. and Med.*, 4: 467, 1932.

<sup>3</sup> Derot, M., *La Créatininémie*. M. Vigne, Paris, 1932.

<sup>4</sup> Rose, W. C., *The Metabolism of Creatine and Creatinine*. *Ann. Rev. of Biochemistry*, 11, 187, 1933.

<sup>5</sup> Kayser, F., *Créatine et Créatinine*. *Chimie. Propriétés. Répartition dans le monde vivant. Rapports avec la biochimie du muscle et du nerf.*, *Actualités Scientifiques et Industrielles*, 178, Herman et Cie, Paris, 1934.

<sup>6</sup> Kayser, F., *Métabolismes des Corps Créatiniques. Variations au cours des États Pathologiques. Actualités Scientifiques et Industrielles*, 179, Herman et Cie, Paris, 1934.

<sup>7</sup> Rose, W. C., *The Metabolism of Creatine and Creatinine*, *Ann. Rev. of Biochemistry*, IV, 243, 1935.

<sup>8</sup> Thomsen, A. Kreatinuri. I. Kommission: Poul Hertz Boghandel Nørregade 35-København, 1938.

<sup>9</sup> Nevin, S. Primary Diseases of Voluntary Muscles, *J. Neurol. and Psychiat.*, 1: 120, 1938.

<sup>10</sup> Terroine, E. F., *Créatine et Créatinine. Actualités Scientifiques et Industrielles*, 600, Herman et Cie, Paris, 1938.

<sup>11</sup> Gammon, G. D., Harvey, A. M. and Masland, B. L., *On the Nature of Certain Diseases of the Voluntary Muscles. Muscle*. Edited by W. O. Fenn, Jacques Cattell Press, 291, 1941.

<sup>12</sup> Beard, H. H., *The Biochemistry of Creatine and Creatinine*. *Ann. Rev. of Biochemistry*, X, 245, 1941.

<sup>13</sup> Beard, H. H., *Creatine and Creatinine Metabolism*. Chemical Publishing Co., Brooklyn, N. Y., 1942.

<sup>14</sup> Wang, E., *Clinical and Experimental Investigations on the Creatine Metabolism*, Mercators Tryckeri, Helsingfors, 1939.

## CREATINE AND CREATININE TESTS

See Bolliger, Deniges, Folin, Hammer, Hofmeister, Jaffé, Kolisch, Pittarelli, Sanchez.

## CREATINE ANHYDRASE

See Creatine and Creatinine Metabolism.

## CREATINE CLEARANCE

See Creatine and Creatinine Metabolism.

## CREATINE COEFFICIENT

See Creatine and Creatinine Metabolism.

## CREATINE ENZYME

### (MILLER AND DUBOS)

See Creatine and Creatinine Metabolism.

See Phosphagen.

## CREATINEMIA

See Creatine and Creatinine Metabolism.

## CREATINE OXIDASE

See Creatine and Creatinine Metabolism.

## CREATINE PHOSPHATE

See Creatine and Creatinine Metabolism.

## CREATINE TOLERANCE

See Creatine and Creatinine Metabolism.

## CREATININE, APPARENT

See Creatine and Creatinine Metabolism.

## CREATININEMIA

See Creatine and Creatinine Metabolism.

## CREATININE OXIDASE

See Creatine and Creatinine Metabolism.

## CREATININE, PREFORMED

See Creatine and Creatinine Metabolism.

## CREATININE, RESIDUAL

See Creatine and Creatinine Metabolism.

## CREATININE, TOTAL

See Creatine and Creatinine Metabolism.

## CREATININE, TRUE

See Creatine and Creatinine Metabolism.

## CREATININURIA

See Creatine and Creatinine Metabolism.

## CREATINURIA

See Creatine and Creatinine Metabolism.

## CREATINURIA,

### PHYSIOLOGICAL

See Creatine and Creatinine Metabolism.



# CREMER REACTIONS FOR PHLORIDZIN

I. Phloridzin yields an amorphous difficultly soluble precipitate upon treatment with benzoyl chloride and sodium hydroxide solution.

II. A solution of phloridzin in 0.1% sodium carbonate forms a red dye with benzene diazonium chloride solution.

III. A red colored substance is obtained when phloridzin is treated with vanillin and hydrochloric acid.

Reference: Zeit. Biol. 36, 115 (1898).

# CRETACEOUS

Chalky; a portion of the mesozoic era between the eocene and the jurassic.

# CRETINISM

Stunted physical and mental development due to failure of thyroid to develop during fetal life, characterized by lowered basal metabolism.

# CRITICAL TEMPERATURE, LOWER

Level of environmental temperature below which the metabolic rate of homeotherms increases with decreasing environmental temperature and above which their metabolic rate is essentially independent of changes in environmental temperature. M. K.

# CRITICAL TEMPERATURE, UPPER

Level of environmental temperature above which an increase in environmental temperature has a thermogenic effect. M. K.

# CROCETIN

$C_{20}H_{24}O_4$ , m.p.  $273^\circ$ , a carotenoid pigment in saffron, occurring as the glycoside alpha-crocine.

# $\alpha$ -CROCIN

A glucoside pigment from saffron, *Crocus sativa*,  $C_{44}H_{64}O_{26} \cdot H_2O$ ; m.p.  $186^\circ$  with decomposition.

# CROSS-BEVAN REAGENT FOR CELLULOSE

Cellulose is soluble in a 30% solution of zinc chloride in concentrated (sp. gr. 1.19) hydrochloric acid.

Reference: Chem. News 42, 77 (1880).

# CROTON OIL

Oil of seeds of *Croton tiglium*, a very powerful purgative; also used for liniments and hair tonics.

# CRUSTACEA

Class of arthropods with numerous appendages, two pairs of antennae, gills, etc.

# CRYOSCOPY

Determination of the properties of substances by freezing points of mixtures.

# CRYPTAL

A terpene aldehyde found in various eucalyptus oils,  $C_{10}H_{16}O$ .

# CRYPTOGAMS

Plants that produce no true flowers or seeds; propagate by spores, e.g. ferns.

# CRYPTOPINE

$C_{21}H_{23}O_5N$ ; prisms, m.p. 220-221; rare alkaloid of opium and several species of *Dicentra*; causes depression of higher brain centers, with ultimate spinal paralysis, damages the heart, and causes convulsions without increasing reflex excitability; is a local anesthetic.

# CRYPTORCHISM

Condition of undescended testes.

# CRYPTOXANTHIN

See Carotenoids.

**CRYSOPHANIC ACID**

4,5-dihydroxy-2-methylanthraquinone; chrysophanol; m.p. 196°, found in cascara sagrada, rhubarb, senna, etc.; used medicinally as Chrysarobin for skin diseases.

**CRYSTALS, LIQUID**

Mesomorphic state; a melt or solution of a crystalline substance which shows orientation, as by double refraction, indicating a shaping or grouping of molecules along different axes which do not show the same optical, magnetic or electrical properties in all directions.

**CUBEBS**

Dried unripe fruits of *Piper cubeba* which yield a volatile oil, used as a urinary antiseptic.

**CUPREINE**

Hydroxycinchonine; ultraquinine; alkaloid of cuprea bark, m.p. 198°, half as toxic as quinine.

**CURARE**

Extract of *Strychnos* containing the alkaloid curarine, South American arrow poison, used to combat tetanus in non-lethal doses.

**CURATIVE DOSE, MINIMUM**

See Chemotherapy.

**CURATIVE RATIO**

See Chemotherapy.

**CURINE**

An alkaloid which lowers the blood pressure and paralyzes the heart.

**CURRENTS, BIOLOGICAL**

See Bioelectric Potentials.

**CUTICLE**

See Hair.

**CUTIS**

See Corium.

**CYANIDE-NITROPRUSSIDE REACTION**

A test for the disulfide (-S-S-) group. The solution to be tested (sometimes saturated with ammonium sulfate) is treated with sodium cyanide and fresh nitroprusside and then made alkaline with ammonium hydroxide. An intense purple color is positive. It is caused by sulfhydryl groups, which are produced from the disulfide groups by the action of cyanide. When sulfhydryl groups are present as such, cyanide treatment is not necessary to cause a positive test (Nitroprusside Reaction).

**CYANIDIN**

See Anthocyanins.

**CYANIN**

A pigment found in the cornflower and rose; it belongs to the group of anthocyanins, and gives on hydrolysis 2 molecules of glucose and one of cyanidin. Other cyanidin anthocyanins are: chrysanthemin or asterin of the chrysanthemum, aster and various berries and peonin from the peony.

**CYANOPHORIC GLYCOSIDES**

Glycosides which yield hydrocyanic acid on hydrolysis, e.g. amygdalin.

**CYANOSIS**

See Dyspnea.

**CYCLITOLS**

A group of carbohydrate-like substances consisting of polyhydroxycyclohexanes, examples of which are inositol and quercitol.

**CYCLOL THEORY**

A theory of protein structures based largely on mathematical probabilities, X-ray studies, and studies of unimolecular protein films. It speaks of a series of

triazine hexagons, built into one another in such a way that "every triazine hexagon is surrounded by three of the triazine hexagons joined by a single diazine hexagon."

### CYCLOPROPANE

Anesthetic used with oxygen, of low cardiac toxicity, but dangerous in use for lack of warning of breakdown.

### CYCLOSES

See Cyclitols.

### CYCLOSIS

The continuous streaming in many plant protoplasts (cells).  
See Protoplasm.

### CYMARIN

$C_{30}H_{44}O_9$ ; a cardiac glucoside which occurs in Canadian hemp and belongs to the digitalis group. On hydrolysis it yields strophanthidin and cymarose, m.p.  $130^\circ$ . Similar glycosides are: periplocymarin which hydrolyzes to periplogenin and cymarose, and sarmento-cymarin which hydrolyzes to sarmentogenin and sarmentose.

### CYMAROSE

$C_7H_{14}O_4$ ; a sugar, 3-methyl-D-digitoxose, obtained by the hydrolysis of cymarin, the active principle of Canadian hemp. It is a desoxy-sugar and has a m.p.  $88^\circ$ . Sarmentose is an isomer.

### CYMENES

Isopropylmethylbenzenes;  $C_{10}H_{14}$ ; occur in many essential oils and in wood (especially p-cymene).

### CYSTEINE

$HS-CH_2CH(NH_2)COOH$ , an amino acid resulting from the reduction of cystine. It is presumably the carrier of the sulfhydryl groups of proteins.

### CYSTEINE AND CYSTINE TESTS

See Andreasch, Dyer-Baudisch, Fleming, Folin-Looney, Hazellopp, Looney, Morner, Okuda-Nishijima, Patten, Sanchez, Sullivan.

### CYSTINE

See also Hair.

### CYSTINE METABOLISM

Cystine, a component of most proteins, is a prominent constituent or precursor of the keratins, glutathione, tunilin, taurine, and taurocholic acid. Only plants can synthesize cystine from inorganic matter, (sulfates, etc.). However, cystine is not an essential constituent of mammalian diet although it is essential in their tissue synthesis because mammalian metabolism can produce cystine from methionine. In normal metabolism excess cystine is destroyed, being excreted chiefly as urinary sulfates.

### CYSTINE REACTION

See Sullivan Reaction.

### CYSTINURIA

An inborn error of metabolism (q.v.) where cystine is excreted in the urine and may be deposited in the form of kidney or bladder stones.

### CYSTITIS

Inflammation of the urinary bladder which takes on acute or chronic forms and may be of gonococcal or tubercular origin. Infections are commonly due to *Escherichia coli*, the staphylococcus, the streptococcus and more rarely proteus vulgaris. Among the predisposing causes are urinary stasis of any origin (calculi, faulty innervation, tumors, etc.). In cautious bladder irrigations or

instillations only very dilute solutions of potassium permanganate, silver nitrate or mercuric chloride are used.

See also Urology.

# CYSTOSCOPY

See Urology.

# CYTASE

A group of enzymes which hydrolyze hemicelluloses, such as e.g. araban, mannan, xylan, galactan. See Enzymes, Non-Proteolytic.

# CYTIDINE

A nucleoside consisting of d-ribose and cytosine, m.p. 230°.

# CYTIDYLIC ACID

3 - cytosine - 3 - phosphoriboside, a nucleotide found in ribonucleic acids.

# CYTISINE

Ulexine, sophorine, baptitoxine, laburnine;  $C_{11}H_{14}ON_2$ ; from the seed of *Cystissus laburnum*; m.p., 152-153°; used as purgative, emetic, diuretic.

# CYTOCHROME

A class of hemochromogens, probably the main factor in respiration, widely distributed in aerobic cells, absent from obligate anaerobic cells. Oxidizable through mediation of Warburg's Ferment; do not combine with cyanide or carbon monoxide at physiologic pH values. Designated, according to position of absorption bands, as cytochrome

a, a<sub>1</sub>, a<sub>2</sub>, a<sub>3</sub>, b, b<sub>1</sub>, b<sub>2</sub>, c, and c<sub>1</sub>. Reduced forms are reoxidized with the aid of cytochrome oxidase.

# CYTOCHROME OXIDASE

An enzyme which catalyzes the oxidation of ferro cytochromes by molecular oxygen; it does not oxidize p-phenylenediamine, is sensitive to HCN and H<sub>2</sub>S and is probably identical with Warburg's respiratory enzyme.

# CYTOFLAV

A yellow water soluble pigment found in some animal tissues. It is riboflavin phosphoric acid ester. In combination with a specific protein it yields Warburg and Christian's "old" yellow enzyme.

# CYTOLOGY

The science of cells, their structure and function.

# CYTOLYSIS

The dissolution or destruction of cells.

# CYTOPHAGAS

See Cellulose Decomposition.

# CYTOPLASM

See Protoplasm.

# CYTOSINE

2-oxy-6-aminopyrimidine; a pyrimidine derivative found in the nucleic acids.

# CYTOSINE, TEST FOR

See Johnson-Clapp, Wheeler-Johnson.

## D

### DAGENAN

See Sulfapyridine.

### DAHLITE

See Bone Salt.

### DAKIN REAGENT FOR ALDEHYDES AND KETONES

Readily crystallizable, water-insoluble products are obtained when aldehydes or ketones are treated with a solution of p-nitrophenylhydrazine in 30 parts of 40% acetic acid. This is a modified Fischer reagent.

Reference: J. Biol. Chem. 4, 235 (1908).

### DAKIN'S THEORY OF TYROSINE METABOLISM

Tyrosine is oxidized to p-hydroxyphenylpyruvic acid, which then splits open its ring, acetoacetic acid being formed; it is, therefore, strongly ketogenic. See Neubaer's theory.

### DAMBONITOL

Dimethyl ether of inositol, found in various latices.

### DAP

Dihydroxyacetonephosphate.

### DARK-FIELD MICROSCOPY

See Protoplasm.

### DATISEIN

See Flavonol Glycosides.

### DEAMINASE

Any one of a group of enzymes which remove an amine group from a compound.

### DEAMINATION

Metabolic removal of amino group from amino acids and the like.

See Amino Acids.

### DECANE,-1,10-DICARBOXYLIC ACID

See Plant Growth Hormones.

### DECARBOXYLATION

The removal of a COOH group, usually by the splitting out of CO<sub>2</sub>.

### DECHOLIN

A trade name for sodium dehydrocholate, injected in diseases of the liver and bile passages.

### DECIDUA

Mucous membrane of uterus which hypertrophies toward the end of menstruation or birth.

### DECIDUOUS

Shedding at the end of growth; opposite of evergreen.

### DE CONINCK REACTION FOR PHENYLGLYCINE

An aqueous solution of phenylglycine is treated successively with equal volumes of concentrated sulfuric acid twice at an interval of a few moments. The heat evolved

causes the formation of a violet color gradually changing to brown at the bottom of the vessel; simultaneously an odor of bitter almonds is perceived and two layers form, the upper being colorless, then turbid and finally yellow.

Reference: Compt. rend. 1903, 1470.

## DECOSE

Any monosaccharide with the formula  $C_{10}H_{20}O_{10}$ ; there are none naturally occurring.

## DEHN-SCOT TEST FOR HIPPURIC ACID IN THE PRESENCE OF UREA

A few cc. of urine are treated with an excess of sodium hypobromite solution (bromine in sodium hydroxide) and the mixture heated to decompose the urea. Depending upon the concentration of hippuric acid, a smoky pale red color or an orange to brown-red precipitate is formed.

Reference: J.A.C.S. 1908, 1418.

## DEHYDRASES

See Dehydrogenases.

## DEHYDROANDROSTERONE

See Isodehydroandrosterone.

## DEHYDROCHLOROPHYLL

See Chlorophyll.

## 7-DEHYDROCHOLESTEROL

See Radiation, Biological Effects of.

## DEHYDROCORYDALINE

$C_{22}H_{23}O_4N$ ; yellow crystalline powder, m.p. 112-113°; alkaloid of the roots of Corydalis; formed by oxidation of Corydalin; causes fall in blood pressure.

## DEHYDROGENASE

(1) An enzyme which activates the hydrogen of metabolites; it is aerobic, like xanthine dehydrogenase, when it can use molecular

oxygen directly, or anaerobic, like lactic dehydrogenase, when it can use oxygen only through the intermediation of another system; experimentally the activity is shown as the ability to oxidize a given metabolite in the absence of air and reduce dyes of the proper potential.

(2) The complete enzyme system necessary for the activation of the substrate in cases where more than one component is involved (D. E. Green).

## DEHYDROGENASES

Enzymes found widely distributed in the tissues which activate molecules of metabolites so that they can be oxidized by a hydrogen acceptor.

## DEHYDROGENASES (CLASSIFICATION)

1. Aerobic, e.g. xanthine oxidase, d-amino acid dehydrogenase, tyramine dehydrogenase, uricase, which require neither coenzyme or cytochrome systems.
2. Anaerobic, which are:
  - a. Cytochrome-linked, e.g. succinic and alpha-glycerophosphate dehydrogenases;
  - b. Cozymase-linked, e.g. lactic, malic, beta-hydroxybutyric, citric, glucose, alcohol, triose phosphate, dihydroxyacetone, l(+) glutamic dehydrogenases and aldehyde mutase;
  - c. Coenzyme II-linked, e.g. glucose and hexose monophosphate dehydrogenases.

## DEHYDROGENASES, CLASSIFICATION OF

Green and Brosteaux classify them as:

1. Aerobic oxidases — react with



molecular oxygen, producing  $H_2O_2$ , e.g. uricase, xanthine oxidase; 2. Cytochrome oxidase—react with oxygen indirectly through cytochrome, but not through flavoprotein, e.g. Warburg's respiratory ferment; 3. Co-enzyme dehydrogenases—react with oxygen indirectly through flavoprotein, but not cytochrome, and require a co-enzyme, e.g. lactic and malic dehydrogenases; 4. Miscellaneous, e.g. aldehydemutase, catalase.

### DEHYDROGENASES, CYTOCHROME REDUCING

Enzymes which catalyze the oxidation of their substrates by hydrogen acceptors, as methylene blue, but not by molecular oxygen; especially active with the 3 cytochromes; include alphasglycerophosphoric dehydrogenase, succinic dehydrogenase, lactic dehydrogenases from yeast and Gonococcus, formic dehydrogenase (Bact. coli), choline dehydrogenase (liver).

### DEHYDROISOANDRO- STERONE

$\Delta^5$  - 3-hydroxyaetioallocholenone-17; m.p.  $138^\circ$ ,  $148^\circ$  (two forms); a subsidiary androgenic hormone found in male urine; Potency  $600\gamma=1$  C.U. (capon unit).

### DELPHINIDIN

See Anthocyanins.

### DELPHININ CHLORIDE

$C_{41}H_{39}O_{21}Cl \cdot 2H_2O$ ; a pigment belonging to the group of anthocyanins, which occur in the flowers of larkspur and many other plants. On hydrolysis it gives delphinidin chloride, 2 molecules of glucose and 2 molecules of p-hydroxybenzoic acid.

### DELPHININ

$C_{34}H_{47}NO_9$ ; A poisonous glycoside of the flowers of larkspur, consist-

ing of 2 molecules of glucose, 2 of p-hydroxybenzoic acid, and one of delphinidin; it is used externally to relieve pain.

### DENATURATION

A reversible change in a protein which always occurs before coagulation. It is characterized by a loss of solubility at the isoelectric points, greater susceptibility to proteolytic enzymes, and a change in the specific rotation. It does not occur without the presence of water. Some groups such as -SH appear for the first time, while some of the more polar groups disappear.

### DENATURATION, LIGHT

See Radiation, Biological Effects of.

### DENATURATION, PROTEIN

See Protein Structure.

### DENDRITES

See Nervous System.

### DENIGÈS METHYLGLYOXAL REAGENT

100 cc. water, 0.6 cc. bromine and 20 gm. 5% glycerine solution are heated in boiling water for 20 minutes, the excess bromine is boiled off and the solution evaporated to 100 cc. Add 20 cc. sulfuric acid to the cooled solution and distil 50 cc.

The substance is mixed with 2 cc. sulfuric acid and 0.4 cc. of distillate giving characteristic colors with a number of substances.

Reference: Bull. trav. soc. pharm. Bordeaux 49,196 (1911). Bull. soc. chim., 5,649.

### DENIGÈS MICRO-TESTS FOR CREATINE AND CREATININE

I. One drop of a saturated solution of about 1 mg. of substance in 1 drop of ammonia; a persistent orange color is obtained with creatinine. Creatine does not cause

any color change. The orange color changes to yellow due to conversion of creatinine to creatine in the alkaline medium.

II. The substitution of a 1% solution of osmium nitroprusside for the picric acid gives rise to a blood-red color with creatinine and a faint rose color with creatine.

Reference: Bull. trav. soc. pharm. Bordeaux 73, 89 (1935).

#### DENIGÈS REACTION FOR CINCHONA ALKALOIDS

0.2 gm. of alkaloid (cinchonidine, cinchonine, cupreine or quinine) are dissolved in 2 cc. glacial acetic acid and 2 cc. sulfuric acid added, producing a fluorescence. The addition of 2 cc. formaldehyde yields a bluish green fluorescence with cupreine and quinine; blue-violet fluorescence with cinchonidine and a blue fluorescence with cinchonine. The cupreine fluorescence disappears with the addition of 3-4 cc. of water.

Reference: Repert. de pharm. 1909, 486. Bull. trav. soc. pharm. Bordeaux, Sept. 1909.

#### DENIGÈS REACTION FOR DIHYDROXYACETONE

0.4 cc. of an aqueous solution of dihydroxyacetone (not more than 0.1%) are mixed with 0.1 cc. 4% potassium bromide, treated with 2 cc. sulfuric acid and 0.1 cc. 5% alcoholic guaiacol solution and heated on a steam bath; a blue-violet color, having an orange absorption spectrum is obtained. The use of salicylic acid in place of guaiacol gives rise to a rose-red color with a yellow and blue absorption spectrum; with gallic acid the color reaction is like that of guaiacol.

Reference: Compt. rend. 148, 172, 282, 422 (1909).

#### DENIGÈS REACTIONS FOR DIHYDROXYPHENYL-ALANINE

I. A brown color is produced when dihydroxyphenylalanine is dissolved in dilute sodium hydroxide. The solution also reduces an ammoniacal solution of silver nitrate.

II. A solution of the substance is shaken with lead dioxide and filtered, yielding a filtrate which is an intense reddish brown.

III. One drop of ammonia is added to a suspension of a few particles of substance in 5 cc. of water, followed by the addition of 10 drops of hydrogen peroxide and heated to boiling; a light brown color develops.

IV. A suspension of the sample in 2 drops of water is treated with 1 drop of sulfuric acid, shaken, and 2 cc. more of acid added plus 1 drop of formaldehyde, giving rise to an intense violet color.

Reference: Bull. trav. soc. pharm. Bordeaux 64, 157 (1926).

#### DENIGÈS REACTION FOR GLUCURONIC ACID

0.4 cc. of an aqueous solution of the acid is treated with 0.1 cc. of a 5% alcoholic solution of codeine and 2 cc. concentrated sulfuric acid and heated on a water bath for 5 minutes; a reddish-purple color, with an absorption band in the yellow and green spectrum, is obtained.

Reference: Bull. trav. soc. pharm. Bordeaux 50, 292 (1912).

#### DENIGÈS REACTION FOR TYROSINE

1-2 drops of tyrosine solution are added to a mixture of 3-5 drops of a 33% alcoholic solution of acetaldehyde and 2 cc. of sulfuric acid, producing a red color even in dilutions of 1.10000.

1 cc. formaldehyde in 50 cc. sul-

furic acid may be used; warming the solution to 50-60° with tyrosine gives a rust-brown color gradually changing to reddish. Boiling the solution with twice its volume of glacial acetic acid causes a color change to green. Reference: Bull. trav. soc. pharm. Bordeaux 1900, 135. Compt. rend. 1900, 583.

#### DENIGÈS REACTIONS FOR PYRROLE

I. A mixture of 5 cc. 0.01% pyrrole solution, 0.3 cc. 5% sodium nitroprusside solution and 1 cc. sodium hydroxide becomes greenish-yellow, then green. A blue color is obtained when the solution is boiled and treated with 1 cc. glacial acetic acid.

II. The addition of 2 cc. hydrochloric acid to the mixture used above gives rise to a red color on boiling.

III. A mixture of 5 cc. alcoholic pyrrole and 5 cc. concentrated hydrochloric acid, on being treated with an alcoholic vanillin solution, forms a reddish-yellow color.

Reference: Bull. trav. soc. pharm. Bordeaux 48, 65 (1910). Zeit. physiol. Chem. 75, 232 (1911).

#### DENIGÈS REAGENT FOR ALDOSES AND KETOSES

Twenty cc. of a solution of 10 gm. crystalline sodium acetate in 5 cc. glacial acetic and 100 cc. water are mixed with 3 cc. glacial acetic acid followed by the addition of 1 cc. phenylhydrazine and 1 cc. 10% sodium bisulfite solution to form a very stable reagent.

Reference: Bull. trav. soc. pharm. Bordeaux 52, 513 (1914).

#### DENIGÈS TESTS FOR ACETONE

I. 0.1 cc. of acetone are heated with 10 cc. bromine water for 20

minutes and the excess bromine is then boiled off. 5 cc. of the bromoacetone solution are boiled with 1:100 sodium carbonate solution and 0.4 cc. of this reaction product are treated with 0.1 cc. 1:10 potassium bromide solution, 2 cc. concentrated sulfuric acid and 0.1 cc. alcoholic salicylic acid solution giving rise to a violet to red-violet color at room temperature. Use of guaiacol for salicylic acid produces a blue color.

II. The test solution is treated with an equal volume of reagent (5 gm. mercuric oxide dissolved in 20 cc. of concentrated sulfuric acid and 80 cc. water) and heated on the water bath, a turbidity or precipitate being produced if acetone is present.

Reference: Bull. trav. soc. pharm. Bordeaux 59, 102 (1912). Compt. rend. 126, 1868.

Berlin. klin. Wochsch. 36, 828. J.A. M.A. 1906, No. 11. Bull. soc. chim. 1908, 910.

#### DENIGÈS TEST FOR INDOLE

5 cc. of an 0.2% alcoholic solution of vanillin and 3 cc. concentrated hydrochloric acid are added to 5 cc. of the alcoholic test solution producing an eosin to garnet color with an absorption spectrum in the green and blue. A yellow color is obtained when cinnamaldehyde is used in place of vanillin.

Reference: Compt. rend. soc. biol. 64, 295, 689 (1908). Repert. de pharm. 20, 161 (1908).

#### DENIGÈS TESTS FOR MERCAPTANS

An alcoholic solution of a mercaptan is added to a few cc. of reagent (1 gm. of isatin in 100 cc. concentrated sulfuric acid) previously diluted with several volumes of concentrated sulfuric acid; a green color is produced. Aldehydes and

higher alcohols are removed, if present, by shaking with sodium nitroprusside; a red color forms. Reference: J. pharm. chim. 1889, 276. Compt. rend. 108, 350 (1889). Ann. 1892, 379.

#### DENIGÈS TEST FOR PHENOLIC ALKALOIDS

The following colors are produced when the substances are treated with a solution of titanium in hydrochloric or sulfuric acid: apomorphine, violet-red; cupreine, bright red; hordenine, dark orange-yellow; morphine, blood red; oxydimorphine, wine-red. No reaction is given by alkaloids without phenolic groups.

Reference: Bull. soc. chim. 19, 308 (1916).

#### DENIGÈS TEST FOR SULFANILIDS

A mixture of several mg. of substance and 0.02-0.03 gm. of potassium ferrocyanide are gently heated for 20-30 seconds in a dry tube; an odor of mercaptans is a positive test.

Reference: Bull. trav. soc. pharm. Bordeaux 71. 5 (1933). Bull. trav. soc. pharm. Bordeaux 73, 89 (1935).

#### DENITRIFICATION

The removal of nitrogen from inorganic nitrates, nitrites and hypoxinites by bacterial action.

#### DENTIN(E)

See Teeth, Biochemistry of.

#### DEOXYCHOLIC ACID

See Desoxycholic acid.

#### DEPHOSPHORYLATION

See Phosphate Bond Energy.

#### DEPRESSANTS

See Pharmacology.

#### DESAMINOCOENZYME

A reaction product of coenzyme I with nitrous acid, which shows

some of the activity of the original coenzyme.

#### DESEPTYL

See Sulfanilamide.

#### DESMOAMYLASES

Insoluble amylases of the cell.

#### DESMOLYZING ENZYMES

Enzymes concerned in fermentation.

#### DESMOTRYPSIN

The inactive tryptic material left in the pancreas after glycerol extraction. It is activated to trypsin by enterokinase. There are apparently 2 fractions, an  $\alpha$ -fraction, lyotrypsin, soluble in electrolytes a  $\beta$ -fraction, soluble only in dil. HCl or  $\text{Na}_2\text{CO}_3$ .

#### DESOXYCHOLIC ACID

$\text{C}_{24}\text{H}_{40}\text{O}_4$ ; m.p.  $176^\circ$ ; a bile acid found in man, ox, goat, sheep, deer and antelope. It is 3, 12-dihydroxy-cholanic acid. Also deoxycholic acid. H. S.

#### DESOXYCORTICOSTERONE ACETATE

A synthetic preparation used instead of natural adrenal cortex hormones in diseases associated with hypo-adrenal cortex function, as Addison's disease. The synthetic preparation does not always substitute completely for the natural. Even small doses may affect the circulatory system, causing hypertension and cardiac decompensation.

#### DESOXY-SUGARS

Sugars in which one or more hydroxyl groups are replaced by hydrogen, e.g. 2-desoxy-d-ribose of animal nucleic acid.

#### DESQUAMATION

Shedding (of skin) in flakes.

#### DES-THIO-BIOTIN

Biotin without sulfur, the place

of the sulfur being taken by two hydrogen atoms; is oxidizable to pimelic acid.

## DETOXICATION

Detoxication is the term applied to the chemical reactions employed by the organism to render toxic agents innocuous or to facilitate their elimination. In a broader sense, however, the detoxication reactions include all the chemical changes that occur in a foreign compound taken into the body.

Toxins are of two types: (1) those produced by the bacteria of the intestines and (2) harmful foreign substances taken into the body, usually by the oral route. The main products of intestinal putrefaction are amines from the decarboxylation of amino acids; aromatic acids from the deamination of cyclic amino acids; and phenols which are likewise the end products of bacterial action on amino acids. Specific examples are putrescine from arginine, cadaverine from lysine, tyramine from tyrosine, histamine from histidine, phenylacetic acid and benzoic acid from phenylalanine, phenol from tyrosine, and skatole and indole from tryptophane.

In the detoxication the noxious agent is either destroyed or the chemical groups responsible for its physiological activity are removed or inactivated. The end products usually possess a higher acidity than the original compound. It appears likely therefore that an important factor is the conversion of a weakly acidic compound which the organism excretes with difficulty to a strong acid which the kidney eliminates with greater ease. Examples are the formation of hippuric acid, a strong acid with an

ionization constant of  $2.3 \times 10^{-4}$  from benzoic acid with  $\text{CH} = 2.3 \times 10^{-5}$ ; and phenol sulfuric acid from the weakly acidic phenol.

It appears likely that the organism employs the same mechanism for detoxication as it does for normal metabolic processes. The conjugation of cholic acid with glycine to form the bile acid, glycocholic acid, is very probably accomplished by the same mechanism which combines glycine and benzoic acid to form hippuric acid. Glucuronic acid which was heretofore considered almost solely as a detoxifying agent is now known to occur combined with various sex hormones. Occasionally the end products are physiologically more potent than the primary substances. Some of the acetylated derivatives of sulfanilamide appear to be more toxic than the parent compounds.

Oxidation is the most important reaction employed by the organism for the destruction of poisons. Many organic compounds of which ethyl alcohol is a typical example are completely oxidized to carbon dioxide and water. Phenyl-substituted fatty acids undergo  $\beta$  oxidation, i.e., oxidation occurs on the  $\beta$  carbon atom and the side chain is progressively reduced by 2 carbon atoms. Ultimately therefore the acids with an even number of carbon atoms yield phenylacetic acid and the odd number, benzoic acid. The aromatic ring itself is fairly resistant to oxidation. Benzene is slowly converted to phenol, polyphenols, and to a small extent to muconic acid. The introduction of a carboxyl group in the aromatic nucleus greatly reduces the toxicity. Thus, the adding of the  $\text{COOH}$  group to phenol yields the relatively non-toxic hydroxy benzoic acids.



Reduction as a detoxication reaction is unimportant. A few isolated examples can be found such as the reduction of chloral hydrate to trichloro-ethyl alcohol which is conjugated with glucuronic acid.

Hydrolysis is occasionally employed in protecting the body against poison. The various glucosides including the digitalis compounds are split into glucose and the aglycone as a preliminary step in their destruction.

Conjugation of compounds foreign to normal metabolic products is widely employed by the body. The coupling of aromatic acids with glycine is a reaction observed even in the lower vertebrate forms such as the frog. Since the body can synthesize glycine readily, large amounts of aromatic acids can be conjugated. The production of hippuric acid from benzoic acid is the best known example of this type of detoxication. Since the liver is an important factor in this conjugation, the rate of synthesis of hippuric acid has become a widely employed test of liver function. The presence of a group ortho to the carboxyl inhibits the glycine conjugation. This ortho blockage which is a biological type of steric hindrance offers a reasonable explanation for the commonly observed physiological potency of ortho-substituted compounds. The list of substances combined with glycine is very large and includes such interesting compounds as nicotinic acid which is now recognized as an important vitamin.

Glucuronic acid is another important detoxifying agent. It can be produced in large amounts presumably from glucose and the glucogenetic amino acids. The com-

pound can combine with aromatic acids, phenols, and alcohols. In the dogs, about two-thirds of the ingested benzoic acid is coupled with glucuronic acid. The free or uncombined acid is metabolized with difficulty and cannot be utilized for detoxication.

Sulfuric acid is conjugated with phenols to form the ethereal sulfates normally found in the urine. Indican, the potassium salt of indoxyl sulfuric acid is an interesting example of this type of detoxication product. Sulfur in the form of cysteine is also employed for the detoxifying of naphthalene and various halogenated aromatic hydrocarbons such as bromobenzene. The cysteine molecule attaches itself to the benzene ring through the sulfur atom, and the resulting compound is then acetylated. The end product is known as a mercapturic acid.

Acetic acid is employed by the body for the conjugation of compounds with amino groups. The acetylation of the sulfanilamide compounds is of both theoretical and practical importance. Marked variations in the acetylation reactions in different species occur. Thus p-aminobenzoic acid which is acetylated in the organism of man and the rabbit, is conjugated mainly with glucuronic acid in the dog.

Certain conjugations are strictly limited to particular species. Glutamine is conjugated with phenylacetic acid only in man and in the chimpanzee. Ornithine is employed by the avian organism for the detoxication of benzoic acid.

The conjugation mechanisms are no longer considered solely as detoxication reactions. The fact that various hormones have been isolated as conjugated compounds em-



phasizes the importance of these reactions in normal metabolism. A study of the behavior in the body of compounds not completely metabolized but leaving readily recognized end products have been exceedingly helpful in yielding important information concerning intermediary metabolism. It also offers a promising means for studying the relation of physiological behavior and chemical structure.

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#### DETOXIFICATION BY AMINO ACIDS

See Amino Acids, Physiology of.

#### DEVIL'S APPLE

See Stramonium.

#### DEVONIAN ERA

See Paleozoic.

#### DEXTRIN, CELLULOSE

See Cellulose Decomposition.

#### DEXTRINASE

An uncommon name for an enzyme responsible for the partial hydrolysis of starch.

#### DEXTRINS

Intermediate hydrolysis products of starch. They are highly dextrorotatory, water soluble, and are precipitated by alcohol.

#### DEXTRO (d-) ROTATORY

The rotation of the plane of polarized light to the right shown by solutions of certain optically active compounds.

#### DEXTROSE

See Glucose.

#### DEXTROTARTARIC ACID

See Tartaric Acid.

#### DHURRIN

$C_{14}H_{17}NO_7$ ; A glycoside of Sorg-

hum Volgare; consisting of glucose and p-oxymandelonitrile.

#### DIABETES, EXPERIMENTAL

See Carbohydrate Metabolism.

#### DIABETES INNOCENS

See Glycosurias, Non-Diabetic.

#### DIABETES INSIPIDUS

A relatively rare disease involving the excretion of large amounts of pale urine of low specific gravity, traceable to hypofunction of the pituitary and not to disease of the kidney. There is no sugar in the urine but there are signs of water intoxication. The blood pressure raising component, pitressin, of the posterior part and intermediate part of the pituitary, is used therapeutically by injection or as nasal spray or snuff.

#### DIABETES MELLITUS

Hypo-insulinism; hyperglycemia and glycosuria due to impairment of insulin secretion by the cells of the Islets of Langerhans of the pancreas. The onset is gradual and is supposed to be determined by both sedentary conditions of life and those of extreme emotional strain. Symptoms include polyuria (frequent urination), polydipsia (excessive thirst), polyphagia (excessive appetite) and yet loss in weight and strength. Itching (pruritus) is often present.

Numerous tests have been devised for sugar in the blood and urine, for the tolerance of dextrose and the conditions of acidosis and ketosis marked by the appearance of "acetone bodies" in the urine. Treatment attends chiefly to diet. Numerous food tables, test diets, specific diabetic diets have been

developed, directed toward de-sugarization, maintenance and prevention of ketosis and acidosis. In all cases the strain on the pancreas has to be reduced. Consequently the administration of insulin is a very successful palliative, which, however, has to be watched for the prevention of insulin shock. This can be countered by the prompt administration of sugar and in extreme cases, the injection of epinephrine which causes the liberation of sugar. Sometimes both insulin and carbohydrate are administered especially if boils and carbuncles appear.

See Lewis and Benedict Test, Insulin, Wound Healing.

## DIABETES, RENAL

See Glycosurias, Non-Diabetic.

## DIABETOGENIC PRINCIPLES

Two diabetogenic principles, the blood-sugar-raising principle and the ketogenic principle. The former is antagonistic to insulin by possibly acting on nerve centers controlling carbohydrate metabolism, the latter increases the production of acetone bodies, especially beta-hydroxybutyric acid. The latter is also supposed to depress the metabolic rate, reduce blood lipids and increase the specific dynamic action of proteins.

## DIACETIC ACID

See Acetoacetic Acid.

## DIACETYL

Diketobutane; found in bay oil, butter, etc., b.p. 88°; also formed by special fermentation of glucose via methylacetyl carbinol; carrier of the aroma of butter and other foods.

## DIACETYL REACTION

A test for proteins containing arginine. A dilute solution of the material to be tested is made alkaline and then a drop of diacetyl is added. A pink color with a green fluorescence is positive.

## DIACIDURIA

The appearance of dicarboxylic acids in the urine after feeding monoacid saturated glycerides.

## DIALECTRIC CONSTANT

A specific property of substance defined by  $D$  in the equation:

$$f = Q_1 Q_2 / r D$$

$f$  is the force of attraction or repulsion between two charges  $Q_1$  and  $Q_2$ , separated by a thickness " $r$ " of the substance. The dialectric constant of air is taken as unity.

## DIALYSIS

The separation of colloids from crystalloids, by utilizing the fact that the latter diffuse through a semi-permeable membrane. As the distinction between the colloidal state and the crystalloidal state is purely arbitrary, we find that borderline colloids diffuse to some extent, and that borderline crystalloids diffuse very slowly.

## DIAMINE OXIDASE

An enzyme of animal tissues which catalyzes the oxidation of histamine by molecular oxygen with formation of peroxide. May be a flavoprotein. Attacks putrescine, cadaverine and agmatine, but not ethylene diamine.

## DIAMORPHINE

Heroin; diacetyl morphine; used as a sedative; habit-making.

## DIAPYCNOSIS

The penetration of walls of blood vessels by cells leaving the cell walls intact, assumed to be due to

a fluctuation of gel-sol condition of the cell wall.

## DIAPHORASE

See Straub Flavoprotein.

## DIASTASE

One of a group of enzymes which convert glycogen, starch, or dextrans to reducing sugars. Also called amylase.

## DIASTASE TESTS

See Wender Reactions.

## DIASTOLE

Dilation phase in heart's action.

## DIATOMS

Microscopic algae with siliceous walls.

## 3,5-DIBROMOTYROSINE

$C_9H_9O_3NBr_2$ ; an amino acid which according to the criteria of Vickery & Schmidt (1931) is not accepted as a proven protein constituent, although it probably has a very limited distribution.

## DICOTYLEDONS

Plants with two seed-leaves; subclass of angiosperms.

## DIETHYLHEXESTROL

See Estrogens, Synthetic.

## DIETHYLSTILBESTROL

See Estrogens, Synthetic.

## DIETHYLSTILBESTROL

## DERIVATIVES

See Estrogens, Synthetic.

## DIFFERENTIATION

The process of structural change by which cells of a common origin come to differ from one another chemically and physically, and in consequence to assume special functions, during the development of an organism.

## DIFFUSION

The flow of molecules, usually, but

not necessarily, through a membrane.

## DIFFUSION POTENTIAL

When the oppositely charged ions of an electrolyte, having different mobilities, diffuse through a solution or across a membrane because of concentration differences, the mobility difference results in a separation of charge. This in turn produces electrical potential differences, known as diffusion potentials, which act to accelerate the slower and decelerate the more rapid ions so as to reduce the charge separation.

Anomalous accumulation of ions in living systems (e.g., potassium in many types of cells) is sometimes attributed to this effect. However, ionic mobilities affect their distribution only during the non-stationary period of adjustment. The distribution at equilibrium, when there is no net flow, is independent of mobilities. The sole exception to this is the case of ions which participate in chemical reactions, or are adsorbed or desorbed by other components of the system. In this case the equilibrium distribution depends on the ratio of reaction rate (or adsorption rate) to the mobility.

A theory of this sort is that of Theorell (Proc. Nat. Acad. Sci.,) which supposes an anion produced by cellular metabolism and diffusing out of the cell. It thus is supposed to set up a diffusion potential which acts on Na and K. These have different mobilities, and so K will be preferentially accumulated.

On diffusion potentials: Johlin, Introduction to Physical Biochemistry; or most texts of physical chemistry.

On the theory of Theorell and allied theories, see: Electrolyte Balance in the Cell, J. Reiner and S. Spiegelman, to appear shortly.

## DIGESTION

All living organisms essentially maintain their status quo in equilibrium with their environment. This equilibrium is dynamic and involves a continued exchange of energy and materials. The organism takes in potential energy locked in chemical molecules and, by bringing about reactions of these substances, releases and uses this energy. Some of the entering substances, or their reaction products, are also used directly to form part of the material of the body which receives them. The substances which serve both these uses are overwhelmingly the complex organic constituents of other bodies, plant or animal—the usual “foods.” And these are mostly caused to react with oxygen to release energy or are partially split to simpler components which are then recombined to form body structures. (See Respiration.)

Digestion has to do with the prehandling of food substances before they enter the body proper. The essential problem is this: foods are available to the organism as solid masses of substances, the large molecules of which are insoluble in water and cannot penetrate the membranes which surround all cells. Before food can really enter the body fluids or cells (in distinction from being ingested into some cavity, as a stomach, contained in the body but still connected with and essentially part of the outside world) the large masses must be broken up mechanically and the large molecules must be broken up chemically. This rendering soluble

and diffusable of food material is the essence of digestion. The entire digestive apparatus of animals is organized for the mechanical and chemical splitting of foods. Independent plants, which use the sun's energy to build their body substance (the food of other organisms) from small, soluble and diffusible molecules—as water, carbon dioxide, nitrates, and other salts—neither need nor possess a digestive system. Dependent plants, (bacteria, Fungi, insectivorous plants, and the like) which use ready made food as do animals, do have and use digestive mechanisms.

The number and elegance of the digestive devices of an organism vary roughly with its degree of specialization in general and with its position on the evolutionary scale. Bacteria have no special digestive organs or organelles. They simply secrete from their surface digestive substances, enzymes, which dissolve the food outside of the bacterium. The soluble digestive products then diffuse into the bacterial cell and are used. Protozoa usually sweep food particles and water into their bodies, at a fixed or a changed position; and these food vacuoles constitute temporary “stomachs” in which the digestion proceeds. Metazoa have permanent digestive organs, most elaborate in the mammals.

Man's digestive system, or alimentary canal, is a continuous passage through the body, from mouth to anus, with special extensions into accessory secreting organs (glands). Mechanical digestion, depending on muscular movements, begins in the mouth with the action of the teeth and with chewing movements. The tongue and pharynx muscles then toss the chewed food into the gullet

(esophagus), where other muscles pass it to the stomach. Here the muscular walls further churn and mix the food and digestive juice for some hours, and pass the semi-fluid mixture along to the small intestine. Similar churning, mixing, and slow progression over hours occurs down the thirty odd foot length of the gut. By the end of this gamut, all available food has been fully digested and absorbed through the gut wall. The fluid debris then enters and slowly traverses the large intestine, or colon, from which water is reabsorbed. The remaining solid is finally evacuated as feces.

Chemical digestion is far more important than mechanical digestion, it can, indeed, do the whole job alone. As muscles do mechanical digestion, so glands make and secrete the agents which carry on chemical digestion. Each gland pours into some part of the alimentary canal its special juice which contains one or more of the substances which split food molecules. These substances, enzymes, are very specific, each breaking certain chemical links in certain kinds of molecules. Saliva, discharged into the mouth by salivary glands, contains mucus to serve as lubricant and an enzyme, ptyalin, which splits starch molecules to simpler sugars. Gastric juice, formed in glands in the stomach wall, contains strong hydrochloric acid and the enzyme pepsin, which split proteins part way to their constituent amino acids. Into the upper small intestine empty the digestive juice of the pancreas and the liver's bile. The latter helps mix fat with water, and

so aids in its digestion by other enzymes which are in water. Pancreatic juice is the most important and contains enzymes which digest all food types — trypsin further splits proteins, amylase completes starch digestion, and steapsin breaks the fats. Even the upper small intestine contributes special enzymes and enzyme activators.

In all cases, in man or other animals, by simple or complex organs, insoluble food masses are comminuted mechanically and, more important, split chemically by enzymes until soluble fragment molecules are produced. Digestion is then over and absorption brings these fragments to the body cells for metabolism to begin.

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See also Amino Acids, Physiology of.

#### DIGILANIDE A

See Digitalis.

#### DIGILANIDE B

See Digitalis.

#### DIGILANIDE C

See Digitalis.

#### DIGILANIDASE

See Digitalis.

#### DIGINE

See Digitalis.

#### DIGIPURPURIDASE

See Digitalis.

#### DIGITALIN

See Digitalis.

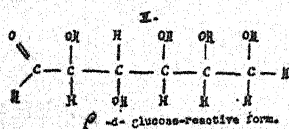
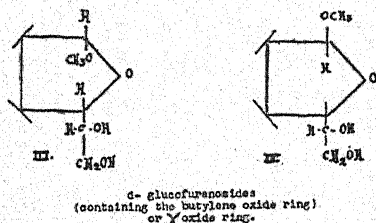
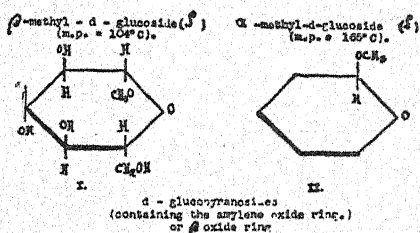
#### DIGITALIS GLYCOSIDES, CARDIO ACTIVE

Under the term of glycosides are included a great diversity of natur-



ally occurring substances and of synthetic products, which are all characterized by their property of yielding various identifiable sugars, along with other chemical compounds, upon acid hydrolysis. Each sugar is, moreover, capable of forming glycosides in more than one way.

The mode in linkage of the sugars with the other component or components, of the glycosides is illustrated, in its simplest expression, by the structure of some of the methyl glucosides formed by the reaction of glucose on hot methyl alcohol in presence of dry HCl gas. The mono-methyl glucosides formed by the most important "forms" of d-glucose<sup>72</sup> are shown in figures I, II, III, IV and V.



Hence the remarkable complexity and difficulties in the analysis of the

glycosides. In the naturally occurring glycosides, the sugar component may reveal any one of its isomeric forms, but also the structure of this sugar component may vary and shift from one form to another according to the origin of the glycoside as well as according to the method used for its extraction and its purification. In what follows the glucidic component of the cardio-active glycosides will be referred to as being of the general form:  $C_6H_{11}O_5$ —, but the reader is reminded that its specific structure will have to be discussed in every case.

It is remarkable that most of the naturally occurring glycosides are levorotatory and hydrolysable by emulsin, thus belonging to the beta-series (pyranosides).

#### Origin of the Cardiac Glycosides:

Since olden times primitive tribes have used, and are still using, for the art of War as well as for the art of healing, various preparations from plants related to the following families: Liliaceae, Ranunculaceae, Asclepiadaceae, Apocynaceae, and Scrophulariaceae: all these plants have a marked effect upon the heart.

The Ranunculaceae furnish the genera: *Adonis vernalis* and *Helleborus niger*, whose glycosides are not yet completely known.

The Liliaceae furnish the genera: *Convallaria mayalis*, containing the convallatoxin,  $C_{29}H_{42}O_{10}$ , made up of glucose and a "genin," and the *Scilla maritima*, studied by Stoll, containing the glycosides: Scillaren A, B, C, which are very similar to the *Digitalis* glycosides.



The Asclepiadaceae include the genus: *Gomphocarpus*, whose root yields the glycoside uzarine, containing two molecules of glucose, and the genus: *Periploca graeca*, containing "periplocin." The genus *Calotropis* furnishes a white sap endowed with energetic digitalis-like properties due to the presence of several glycosides (which see).

The Apocynaceae contain the largest number of cardio-active glycosides, furnished by the genera: *Strophantus*, *Nerium oleander*, *Thevetia neriifolia*, *Cryptostegia madagascariensis*, *Apocynum androsaemifolium*, and a few more of less importance, or less known. *Nerium oleander* contains "oleandrin" formed of "digitalose" and an aglycone "gitoxigenin" also found in the *Digitalis* glycosides. *Thevetia neriifolia* yields "thevetin,"  $C_{29}H_{46}O_{13}$ , whose exact structure is still unknown. *Apocynum androsaemifolium*<sup>61</sup> yields a number of useful substances: acetovanillone, ipuranol, androsterol, homoandrosterol, and two glycosides "apocymarin," containing the sugar cymarose, and "androsyn," which is a very powerful heart tonic and exerts a strong pressor effect, but whose chemical composition is still unknown. *Cryptostegia madagascariensis* has been studied by Raymond-Hamet, Perrot, Mercier, Balansort, and others without much success. It is only known that it contains a water-insoluble glycoside which has been isolated in small amounts, "lombirine," a powerful cardio-active substance.

Finally the Scrophulariaceae are essentially represented by the genus: *Digitalis*, which is discussed at length in the following pages.

Each of the plants considered always contains in variable proportions at least several glycosides of

different physiological activity, which makes the extraction and the purification of definite compounds extremely difficult and explains the extraordinary abundance of "glucosides" reported in the literature, most of them being really mixtures of undefinable composition. For instance *Scilla maritima* has given such preparations as: scillipicrin, scillitoxin, and scillin of Merck, the scillarin of Jarmested and that of Kurtz, the scillipicrin, scillenin, and scillamarin of Waliszewski, the scillitin and scillidiuretin of Kopaczewski, etc. All these substances have recently been resolved into only three initial and well characterized glycosides by Stoll and co-workers: scillaren A, B and C.

Similarly the *Strophantus* genus yielded: cymarin, k-strophantidin-b, amorphous k-strophantidin, allocymarin, periplocymarin, sarmentocymarin, ouabain, uzarin, etc. A discussion of these glycosides will be found in the work of Stoll.<sup>75</sup>

#### Origin of the *Digitalis* Glycosides:

The *Digitalis* glycosides constitute one of the most powerful and indispensable drugs at the disposal of the therapeutists. They exist in more than 18 species of the same genus: *Digitalis*—Linn., (*Scrophulariaceae*), which are at present found in all temperate dry climates of the world, up to Newfoundland. However only three species so far have been extensively used for therapeutic purpose and for the commercial preparation of the drug: *D. purpurea*, *D. lanata*, and *D. ambigua*. The last named species has received only scant attention, and is reported to be less potent than the others.<sup>60</sup> *D. purpurea* is the oldest species employed, and the one most frequently referred to, but its composition is not yet com-

pletely ascertained. *D. lanata*, originating in Central Europe, has been the object of a very thorough study, notably by Stoll and Kreis.

Since 1785, the methods of extracting the drug have been varied, but fundamentally all consist either of a "macerating," or of a "percolation" process, hot continuous extraction in Soxhlet type apparatus being little used for reasons outlined later. The solvents used are: water (Homolle and Quevenne process,<sup>84</sup> or Dutch pharmacopiae of 1927, etc.), diluted alcohol (Tanret method,<sup>80, 81, 82</sup> or relatively concentrated alcohol (Nativelle method;<sup>83</sup> U.S. pharmacopiae of 1877;<sup>89</sup> Perrot and Bourget method;<sup>86</sup> etc.). The physiological properties of the preparations thus obtained vary quantitatively with the solvent used, and practically all these "fluid extracts" are more or less stable, and they lose their potency in a variable length of time (usually 10% or more yearly). It is remarkable however that the most essential properties of the drug, which are exhibited also by some of the crystallized glycosides isolated by modern methods, are qualitatively unchanged, indifferent to the solvent used. This observation leads one to think that the active principles, in the form or combination in which they exist in the living plant, exhibit quite versatile solubility properties, or else that other physiologically inert substances render them soluble in a variety of solvents.

#### Early Attempts at Isolating the Digitalis Principles

The following diagram will give in a condensed form an idea of the complexity of the problem as it appears from a survey of the literature, together with the most important results obtained by the various

workers. The relationships between the various substances mentioned in the literature become obvious when products ultimately found identical are put in a same group (horizontal series).

(TABLE 1 ON NEXT PAGE)

Table I calls for some comments: (a) all the substances mentioned are now recognized as being closely related glycosides. (b) Among them, the digitonin group (digitonin, digitsaponin, gitonin, etc.) is devoid of cardio-active properties: these substances are related to the saponins. (c) The cardio-active principles extracted from *D. purpurea* seeds form a group of their own (digitaline of Schmiedeberg, Digitalinum verum of Kiliani) which is represented by the commercially available "German digitalin."

(d) The other glycosides of *D. purpurea* can be segregated into two groups: the water-soluble substances, which are also quite soluble in alcohol (gitalin, anhydrogitalin, gitoxin, gitogenin) and the chloroform-soluble substances, which are also relatively soluble in alcohol (gitalin, anhydrogitalin, and digitoxin). During the extraction process, the gitalin and anhydrogitalin will part between the digitoxin and the gitoxin fractions, thus rendering their purification rather difficult. Indeed, the "digitaline" of Nativelle has been found by Kraft to contain some 90% of digitoxin and 10% of gitalin and anhydrogitalin, while the "digitoxin" of Schmiedeberg,<sup>71</sup> isolated from the seeds was much purer, although it has the same physiological properties as the Nativelle product.

(e) The substances of table I belong to several distinct groups of bodies, in terms of modern chemical nomenclature, and they are now

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TABLE I.

Homolle (leaf)	Nativelle (leaf)	Schmiedeberg (seeds)	Kraft (leaf)	Kilian (leaf and seeds)	Windaus (leaf + seeds)	Gloetta (leaf)
french amorphous					tannates	
	Digitonine (amorph.)	Digitine	Digitosa- ponin (amorph.)	Digitonin (cryst.)	Gitonin	Gitonin (amorph.)
		Digitaline (amorph.)		Digitali- num verum		
	Digitine		Gitine	Digitalin	Gitogenin	
	Digitaline (cryst.)	Digitoxin	Digitoxin (cryst.) + pseudo- digitoxin	Digitoxin		Digitoxin
			Gitoline + anhydro- Gitalin	Digitalisin	Gitoxin	Digitalinum
	Digitalisin	Digitalisin				
						Gitalin

found to include some of the initial glycosides present in living plant as well as a number of their degradation products, themselves still very complex glycosidic compounds. For instance the "digitalin" of Kiliani,<sup>137-381</sup> or chloroform-insoluble residue of the preparation of digitoxin by the Nativelle method, is the substance called "digitine" by Nativelle. It has been extensively studied by Bourget and Dugue.<sup>9</sup>

These authors determined that, after removal of a small amount of digitonin still present, the residue (their "fraction A") was then much more soluble in chloroform (m.p. 273°, rotation -66.5) and was identical with the "digine" of Tambach<sup>79</sup> and with the "gitogenin" of Windaus and Schneckenburger.<sup>87</sup>  $C_{26}H_{42}O_4$  (m.p. 271°, m.w. 418). This substance yields on hydrolysis an aglycone which has been identified with

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the aglycone of digitonin: the "digitogenin" which upon mild oxidation by the Kiliani method<sup>40</sup> gives the "digitogenic acid" (m.p. 210°), itself further oxidizable by potassium permanganate into a mixture of "digitic acid" (m.p. 203°) and "oxidigitogenic acid" (m.p. 250°). Therefore the initial substance, "digitine" of Nativelle, must be considered as either digitonin or a closely related substance.

The reasons for the similarities established in Table I are shown in abbreviated form in Tables II, III, and IV, which show the relationships between the solubilities and other physical properties, of the various substances reported, and the nature and accredited chemical formula of their most important products of degradation by either acid hydrolysis or oxidation.

TABLE II.

Authors	Glycosides	Degradation products	Formulae	MP :	Observations	Solubility
						H <sub>2</sub> O EtOH CHCl <sub>3</sub>
Kiliani	Digitoxin					
Kraft	Digitoxin					
Nativelle	Digitaline					
Schmiedeberg	Digitoxin	HCl.	$C_{41}H_{74}O_{13}$	240 (260)		• • -
		Digitoxose	$C_6H_{12}O_6$		rotation : +46.3	• •
		Digitoxigenin	$C_{35}H_{62}O_{12}$	230	rotation : +19.1	• •
		Br • digitoxonic acid	$C_6H_{12}O_5$			• •
		isodigitoxigenin		272		•
		HCl				
		alpha • beta anhydrodigitoxigenin	$C_{33}H_{58}O_{10}$	193	rotation : -4.68	•
		H O				
		an acid	$C_{33}H_{56}O_{10}$	167	rotation : +37.3	
		O ketones:				
		KOH	$C_{33}H_{54}O_{10}$	245	rotation : +37.3	• -
		iso-ketone	$C_{33}H_{54}O_{10}$	264	rotation : +19.5	• -
Jacobs		dihydro-digitoxin	$C_{41}H_{76}O_{13}$	202	rotation : +2.4	
		iso-digitoxigenon		272		
		KOH				
		digitoxigenon	$C_{33}H_{54}O_{10}$	245		• -

THE DEGRADATION PRODUCTS OF DIGITOXIN .

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## TABLE III.

Authors	Glycosides	Degradation products	Formulae	MP.	Observations	Solubilities		
						CHCl <sub>3</sub>	EtOH	H <sub>2</sub> O
Nativelle	Digitonin		$C_{55}H_{90}O_{19}$		Saponin	+	+	+
Kraft	"							
Schmied.	Digitine	Digitoresin			saponin	+	+	+
		+						
		Digitonein						
Windaus		Gitonin	$C_{49}H_{80}O_{23}$		saponin	+	+	+
Tambach		↓						
		Digine			saponin	+	+	+
		↓						
		dextrose +						
Nativelle		Digitine				+	+	+
		↓						
Kraft		Gitine						
Windaus		Gitogenin		195	Di-carboxy,	+	+	+
		↓ $Cr_2O_3$						
		Gitogenic acid	$C_{26}H_{40}O_6$	242				
		HCl :						
		1 dextrose +	$C_6H_{12}O_6$			+	+	+
		2 galactose	$C_6H_{12}O_6$			+	+	+
		1 xylose				+	+	+
		1 digitogenin	$C_{26}H_{42}O_5$		genin.	+	-	-
		↓ $Cr_2O_3$						
		digitogenic acid	$C_{26}H_{38}O_7$	210		+		
		↓ KOH			I-Keto-2-carboxy			
		iso-digitogenic acid			I-Keto-2-carboxy	+		
		↓ $KMnO_4$						
		oxidigitogenic acid	$C_{26}H_{38}O_9$	250	I-Keto-3-carboxy	+		
		↓ $KMnO_4$ alk.						
		digitic acid		203	I-Keto 2-carboxy	+		
		↓						
		Ketone +	$C_{26}H_{38}O_4$		revised (see later).	+		
		igitogenin						
		↓ $O_2$						
		iso-sarsapogenone						
		↓ $H_2$						
		iso-sarsapogenone						

THE DEGRADATION PRODUCTS OF DIGITONIN .

(TABLE 4 ON NEXT PAGE)

The "gitalin" of Kiliani appears to be an impure form of "gitoxin" containing some of the true "gitalin" isolated by Cloetta.<sup>17</sup> The anhydrogitalin of Kiliani must be considered also a mixture containing

the dehydration products of gitoxin and Cloetta gitalin.

The known series of degradation products of the *D. purpurea* glycosides reveal no specific substance derived from the cardioactive "digi-

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talein" of Nativelle, and of others.

Summarizing, *D. purpurea* seeds seem to contain one specific glycoside: Digitalinum verum, and *D. purpurea* leaves four specific glycosides: digitonin (devoid of cardio-active properties), digitoxin, gitoxin, and gitalin (of Cloetta).

This species has been extensively studied only recently. A number of

bastards of doubtful descent have been reported in the literature: lanadigine No. I, II, III, and IV of Mannich and co-workers,<sup>56</sup> mixture of digitoxin, dilanin and digoxin of Perrot, Bourcet and Hamet, gitoxin of Smith,<sup>74</sup> etc.

The work of Stoll and his collaborators has revealed that fresh *D. lanata* leaves contain neither of

TABLE IV.  
Down: DEGRADATION PRODUCTS OF  
DIGITALINUM VERUM

Authors	Glycosides	Degradation products	Formulae	MP.	Observations	Solubilities
Schmiedeberg Kilian	Digitalin <i>D. verum</i>	$\xrightarrow{H_2}$ dihydro-digitalin $\xrightarrow{H_2}$ glucose + digitalose + digitaligenin $\xrightarrow{H_2(Pt)}$ dihydro-digitaligenin $\xrightarrow{H_2(Pt)}$ tetrahydro-digitaligenin $\xrightarrow{H_2(Pt)}$ hexahydro-digitaligenin $\xrightarrow{Cr_2O_3}$ hexahydro-digitaligenone $\xrightarrow{Zn-Hg}$ a lactone :	$C_{27}H_{44}O_{14}$ $C_{27}H_{42}O_{13}$ $C_{27}H_{40}O_{12}$ $C_{27}H_{38}O_{11}$ $C_{27}H_{36}O_{10}$ $C_{27}H_{34}O_9$ $C_{27}H_{32}O_8$	211 194 187 205 168	monoxylactone ketone	• • • • • •
		$\xrightarrow{H_2O}$ dianhydrogitoxigenin $\xrightarrow{HCl(EtOH)}$ gitoxigenin : • two digitoxose • three digitoxise	$C_{27}H_{40}O_{12}$ $C_{27}H_{38}O_{11}$ $C_{27}H_{36}O_{10}$	224 102	hydrate of gitoxigenin rotation : 46.3	
Cloetta	gitalin	$\xrightarrow{H_2O + HCl}$ gitoxin	$C_{27}H_{38}O_{11}$ $C_{27}H_{36}O_{10}$	150 266	rotation : -25.2 trioxylactone	• • • • • •

Up : DEGRADATION PRODUCTS OF GITOXIN  
AND OF GITOXIN.



the substances enumerated above, but a constant proportion of only three genuine glycosides: the "lanatosides A, B and C," in combination with glucose and tannic acid, and containing an acetic acid residue in their molecule. Further, the same investigators have shown that similarly, the fresh *D. purpurea* leaves contain none of the substances listed in the above tables, but a constant proportion of three glycosides slightly different but closely related to those of *D. lanata* from which they differ by the absence of acetic acid residue.<sup>76-78</sup> All these glycosides can be isolated relatively easily under conditions preventing both enzymatic and hydrolytic decomposition which are responsible for the greater number of substances isolated from both species by the conventional methods employed by previous workers. This important discovery has been made possible by the isolation of the glucose-splitting enzyme in the laboratory of Willstätter<sup>78</sup> in 1935. This enzyme is left in the cell stroma of the leaves after complete aqueous extraction followed by alcoholic (or acetic) extraction and ether extraction. The residual powder forms a very active suspension in water but is almost inactive in alcohol. Toluene does not affect it. It seems to be a protein destroyed by heat and by the proteolytic ferments and is an amphoteric substance endowed with buffer properties. It is precipitated by high concentration of neutral salts, and by the salts of the heavy metals. This enzyme is somewhat species-specific, hence the distinction between "digilanidase" and "digipurpuridase."

For the sake of brevity, the relationships between the initial

glycosides of *D. lanata*,\* those of *D. purpurea*, and their most important physiologically active degradation products, are diagrammatically presented in Tables V and VI which are abstracted from Stoll.<sup>75, 78</sup>

(TABLE 5 ON SUCCEEDING PAGE)

(TABLE 6 ON SUCCEEDING PAGE)

### The Structure of the Cardio-active Digitalis Glycosides

It has been seen that the hydrolysis (by HCl in alcohol of various strength) of the glycosides always yields, in addition to various sugars, a rather large molecule which can be further split into smaller fragments: this large molecule is called the "aglycone," and is characteristic.

The structure of the aglycones is related to that of the sterols. Grossly, it is formed of a sterol to which is attached both a desoxy-sugar and a lactone ring which seems paramount in enhancing the cardio-active properties of these substances. In order to arrive at a comprehensive picture of these molecules, it has been necessary to perfect (a) special analytical procedure to identify the essential parts of their structure (sugar, desoxysugars, glycosidic linkage, sterol nucleus, lactone ring) and (b) analytical procedures for the glycosidic linkage, sterol nucleus structure and lactone ring structure.

The identification reactions for desoxycarbohydrates are:

I. Keller reaction: the material is slowly warmed in strong HCl; digitalin gives a precipitate, digitonin develops a blue color, and digitoxin a green color.

II. Lafon reaction:<sup>46</sup> about 1 mg. of material is dissolved in 1 cc. of equal weight of conc. sulfuric acid

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TABLE V.

*Digitalis lanata*

*Digitalis. purpurea*

Digilanid A	enzym. →	alpha and beta acetyldigitoxin plus glucose	
	CaO →	deacetyldigilanid A + acetic acid	= purpurosides A
Digilanid B	enzym. →	alpha and beta acetylgitoxin plus glucose	
	CaO →	deacetyldigilanid B + acetic acid	= purpurosides B
Digilanid C	enzym. →	acetyldigoxin plus glucose	
	CaO →	deacetyldigilanid C + acetic acid	= _____
		_____	Citalin
		_____	Diginin
		_____	Digitalinum verum

## THE RELATIONSHIP BETWEEN INITIAL GLYCOSIDES OF DIGITALIS LANATA AND DIGITALIS PURPUREA.

and ethyl alcohol and slowly heated until it gets slightly brown; then one drop of 1 % ferric chloride is added; only digitoxin (french digitaline) develops a green color.

III. Berthelot phosphoric acid reaction:<sup>4</sup> concentrated cold phosphoric acid produces a green color with digitoxin. The color turns yellow on addition of water.

IV. Berthelot chloral reaction:<sup>4</sup> A solution of digitoxin in anhydrous chloral is yellow-green and turns violet and then deep green

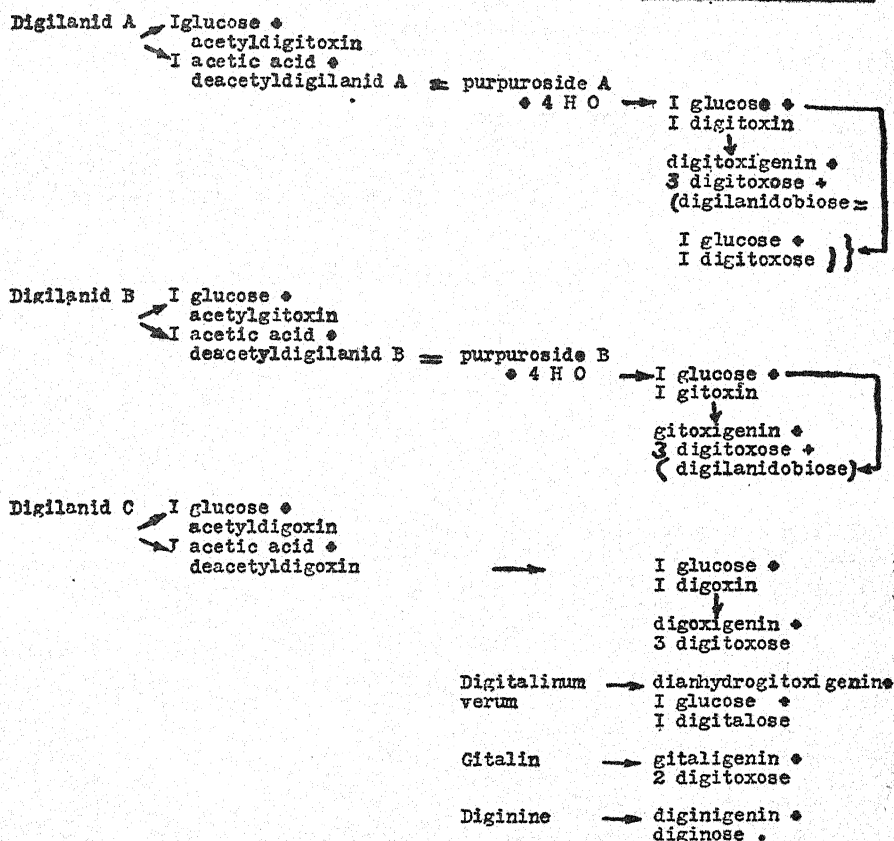
on careful heating.

V. Schmiedeberg reaction:<sup>71</sup> (a) a solution of the material in dilute sulfuric acid slowly heated develops a pomegranate-red color with digitonin; (b) the same reaction carried out with conc. sulphuric acid gives the same color plus a precipitate, and the color turns yellow on addition of bromine. None of the other saponins give the reaction.

VI. Rojahn and Struffman reactions:<sup>67</sup> (a) an alcoholic solution of the material additioned of Marquis

# DICTIONARY OF BIO-CHEMISTRY

TABLE VI.



Glycosides of *Digitalis lanata* .      Glycosides of *Digitalis purpurea* .

Interrelationships of the degradation products of  
the *Digitalis lanata* and *Digitalis purpurea*  
initial glycosides .

formalin-sulfuric acid mixture takes an orange color on warming; (b) the mandelin vanillin sulfuric acid takes a yellow-brown color on warming. If the same reaction is carried in the fashion of a layered test, a blue-brown ring is obtained with the water-soluble digitalis gly-

cosides. If the reagent is applied on the solid material, the water-soluble glycosides develop a violet-brown color while digitoxin crystals take dark orange color; (d) concentrated sulfuric acid becomes yellow with all the digitalis glycosides, on slow warming.

VII. Morel and Marthoud reaction:<sup>62</sup> an alcoholic solution of the material is added to its volume of a solution in 95% alcohol of very pure meta-dinitrobenzene; after cooling, very cold 10% sodium hydroxide solution is added dropwise: the cardio-tonic glycosides develop a deep blue color which fades out on heating.

VIII. Kiliani reaction:<sup>36</sup> the material is dissolved in glacial acetic acid saturated with ferric sulfate, and stratified over a layer of 33% sulfuric acid containing .07% of ferric sulfate: the two layers must remain colorless for at least 30 minutes. When the preparation is progressively heated to 70° a ring forms, whose color shifts from green to blue in presence of desoxycarbohyrates. The color is partly soluble in chloroform, but is not persistent in this solvent.

These reactions are quite specific if the proper precautions are taken. In complex mixtures or crude plant extracts, preliminary procedures are generally necessary to remove pigments and interfering impurities.<sup>1</sup> Crude extracts must be decolorized by the following procedure which we have tested: add  $\frac{1}{2}$  volume of 10% neutral lead acetate to the neutralised alcoholic solution and filter after a few minutes; adjust the alcohol concentration to 50% if necessary; remove the traces of lead with  $H_2S$ ; shake twice with  $\frac{1}{2}$  volume of benzene; evaporate to dryness in vacuum and test the dry residue as said above. For greater specificity the Stas Otto method modified by Rojahn and Struffman<sup>67</sup> can be applied: (a) the material is shaken out of its tartaric acid solution with chloroform; or (b) it is shaken out of its solution in saturated NaCl or  $AmSO_4$

with chloroform containing 10% of alcohol. In both cases the chloroform solution is dried by filtration over fused sodium carbonate and evaporated to dryness before testing. An alternate method described by Burmann can also be used: the chloroformic solution obtained above is shaken with a mixture of equal parts of ether and alcohol; the ether-chloroform layer is separated, evaporated, and the residue tested.

IX. Reducing properties. They can be tested with Fehling's solution. Some desoxycarbohyrates reduce the reagent only at the temperature of boiling. If the material is not soluble in water, alcohol up to 50 or 60% can be used. Some desoxysugars also reduce the Tollens reagent, and so do some of the aglycones.

It should be stressed that, while the above reactions are positive with free desoxycarbohyrates, the mode of glycosidic linkage as well as the nature of the aglycone to which they are bound sometimes considerably change their behavior, and some of the reactions can be attenuated or even blotted out.

In the course of the purification of the glycosides, it is necessary to remove the tannic acid in combination with them. The reaction is carried out in 50% alcohol, by stirring in the cold with lead or zinc oxide. The tannoid combinations of the various glycosides present greater difference of solubility in various solvents than the pure glycosides, and therefore the fractionation is advantageously carried out before the removal of the tannic acid. The end of the reaction with the metal oxide is ascertained by the Berthelot spot test with aqueous 1% ferric chloride, which leaves a

blue ring on the filter paper in presence of combined or uncombined soluble tannoid substance.<sup>4</sup>

The identification reactions for the unsaturated lactone ring of the digitalis aglycones are as follows:

I. Legal nitro-prusside reaction (Jacob et al.<sup>34</sup>), modified by Elderfield<sup>34</sup> about 12 mg. of material are dissolved in alcohol or pyridine; then 3 drops of 10% HCl and 1 drop of .5% sodium nitro-prusside in water are added and dropwise a solution of 10% sodium hydroxide, with an interval of two minutes between each drops so as to permit the observation of the developing color: the beta-gamma lactones give a deep red color fading to a persistent orange; the alpha-beta lactone give a deep red color completely fading out in one second. After alkalization, if one adds dropwise some more nitro-prusside reagent: the beta-gamma lactones show no change of color; the alpha-beta lactones show a transient red color always fading out in a few seconds until no more color is formed, the lactone ring being all oxidized. On re-acidification the beta-gamma lactones give a green color, the alpha-beta lactones give a pure blue color.

II. Potassium ferricyanide test modified by Elderfield:<sup>34</sup> on proceeding exactly as above, using a 1% solution of potassium ferricyanide, during the alkalization the beta-gamma lactones give a clear pink solution; the alpha-beta lactones give a pale brown solution. During the second addition of reagent: the beta-gamma lactones solution remain unchanged; the alpha-beta lactones solution develops a persistent red-brown color.

III. Baljet reaction:<sup>2</sup> the solution

of the crude material, decolorized with lead acetate as for the identification of the desoxycarbohydrates, is mixed with one volume of alkaline picric acid solution in water. A deep orange-red color develops which is due to the presence of an active hydrogen atom in a beta-gamma lactone ring.

After hydrogenation of the glycosides, the double bond of the lactone ring becomes saturated and the above reactions become negative (Jacob and Hoffman).<sup>35</sup>

IV. Acid titration. Under certain conditions the lactone ring opens and forms an acid which can be titrated with NaOH in presence of phenolphthalein.

V. Lactone titration. The lactone ring can be quantitatively estimated by back titration with sulfuric acid after short refluxing (15 to 60 minutes) of the material with an excess of normal sodium hydroxide.

VI. Lactone double-bond titration. Only the beta-gamma lactones consume bromine when treated by the Winkler's method in glacial acetic acid (Jacobs et al.).<sup>33</sup>

VII. Active hydrogen. It is titrated by the Zerevitinoff method using the Grignard reagent. The technique has been adapted by Hans Meyer.<sup>59</sup>

VIII. Acid-lactone transformation. For the sake of identification, it is often desirable to effect this transformation on some of the degradation products of the glycosides which possess a carboxyl. The transformation takes place when the solution of the material in concentrated HCl is left standing at room temperature or a little above. After dilution with water the lactone usually precipitates.

IX. Hypobromite oxidation. The material (0.5 gm.) is treated for 1 hour at room temperature with 10 cc. of 2% NaOH containing 0.25 gm. of Br. On acidification to Congo red with HCl the resulting lactone precipitates.

X. Potassium permanganate oxidation in acetone (very mild). The material (4 gm.) dissolved in dry acetone (100 cc.) is stirred with 4 gm. of potassium permanganate at 0° C. for 3 hours or more under anhydrous conditions. The precipitate containing MnO<sub>2</sub> is extracted with water and the reaction products are precipitated by acidification with HCl.

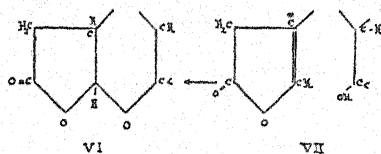
XI. Permanganate oxidation in water. This more energetic reaction is carried out exactly as above, but in presence of ammonia.

XII. Chromic acid oxidation. The material (5 gm.) is dissolved in 70 cc. of dry acetic acid and the oxidation is obtained with 15 cc. of the Kiliani reagent (40): water 400 cc., sulfuric acid: 80 gm., chromic acid 53 gm. The temperature may vary from 0° to about 60° C. After reaction, the solution is diluted to 1 liter, saturated with AmSO<sub>4</sub> and the precipitated ketones collected. The unreacted excess of Cr<sub>2</sub>O<sub>3</sub> can be back titrated for quantitative work.

XIII. Lactone benzoate. For the sake of identification the crystalline benzoate of the lactone can be formed as follows: the material is dissolved in dry pyridine and benzoyl chloride is added. After 5 hours or more at room temperature the mixture is poured into 10% sulfuric acid. The separated oil is extracted with chloroform, washed with cold water and with 10%

sodium carbonate, dried over sodium sulfate, concentrated in water and finally crystallized.

XIV. Anhydrous saponification. One uses normal NaOH in absolute alcohol. This saponification transform the lactone ring into an oxide ring, according to formulae VI and VII:



On re-acidification with CH<sub>2</sub>N<sub>2</sub> one obtains the iso-aglycones in which the lactone ring is saturated.

XV. Catalytic hydrogenation. Any standard quantitative procedure carried out at room temperature at ordinary pressure, gives information about the number of double bonds in the side lactonic chain.

The most important reactions for the sterol nucleus are:

I. The Iodine test: The dry material is dissolved in ice cold 80% sulfuric acid. On adding 1 drop of 1% iodine in KI, a pink color develops.

II. Salkowski reaction. A 1% solution of the material in dry chloroform is stratified over a layer of concentrated sulfuric acid. A fluorescent ring forms. This reaction must not be confused with the one given by the desoxycarbohydrates.

III. Modified Liebermann-Burchard reaction. A chloroformic solution of the material is added to 5 volumes of acetic anhydride and 1 volume of concentrated sulfuric acid. The color takes 24 hours to develop. The reaction is positive with all the digitalis glycosides.



According to Bloor<sup>7</sup> it would afford a quantitative estimation.

IV. Rosenheim reaction. The dry material is dissolved in dry chloroform and one adds one volume of 90% trichloreacetic acid in water. The color and the rate of color development (24 hours) depends upon the number of double bonds in the sterol nucleus. The reaction is negative with most of the digitalis glycosides, but is positive with some of the aglycones or their degradation products.

V. Pettenkofer reaction, modified by Leulier and Griffon.<sup>50</sup> Dissolve the material in 0.5 cc. of absolute alcohol. Add 1 cc. of 1% furfural in 95% alcohol and stratify over a layer of concentrated sulfuric acid. The digitalis glycosides develop a violet-grey color slowly. The modification of Chiray and Cuny,<sup>18</sup> using phosphoric acid is sometime advantageous.

It must be noted that none of the color reactions for sterols are specific, and that they are good only for preliminary identification.

The structure of the sterol nucleus (29, 44, 31, 85, 72, 20, 57) of the lactone ring (58, 64, 33, 83, 28) isomerization under the influence of KOH (27, 64), the dehydration products of the aglycones (31, 26), the glycosidic linkage and the deoxysugars (52, 53, 5, 6, 42, 60, 17, 86, 90, 55, 70, 47, 51. 90. 36. 43. 72) are referred to in the bibliography.

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## BIBLIOGRAPHY

- <sup>1</sup> Anon. Pharm. zent. Monats. 10: 204, 1929.
- <sup>2</sup> Baljet, Henk. Schweiz. apoth. Ztg. 56: 71-73 and 84-88, 1918.
- <sup>3</sup> Batterman, Robert C., Holman, De-lavan V., and DeGraff, Arthur C. Ann. Int. Med. 14: 2058-72, 1941.
- <sup>4</sup> Berthelot, M.P.E. and Jungfleisch, E. Traite elementaire de Chimie organique. Paris. Dunod ed. 2nd ed. 1881.
- <sup>5</sup> Bergmann, Max, Shotte, Herbert, and Leschinsky, Wolfgang Ber. 55: 158-72, 1922.
- <sup>6</sup> Bergmann, Ber. 56: 1052-59, 1923.
- <sup>7</sup> Bloor, W. R. J. Biol. Chem. 24: 227-31, 1916.
- <sup>8</sup> Bockmuhl, Max, and Ehrhart, Gustav, U. S. Patent 2189723, 1936.
- <sup>9</sup> Bonisteel, W. J., J. N.Y. Botan. Garden 43: 89-95, 1942.
- <sup>10</sup> Bornemann, John A., Am. J. pharm. 84: 546-53, 1913.
- <sup>11</sup> Bourget, P., and Dugue, G. C.R. Ac. des Sc. 186: 395-7, 1928.
- <sup>12</sup> Burmann, James, Schweiz. Woch. f. chem. u. pharm. 50: 153-6, 1912.
- <sup>13</sup> Carlinfanti, E., and Marzocchi, P., Boll. chim. farm. 50: 609-15, 1912.
- <sup>14</sup> Charlton, Wm., Hamorth W. N., and Peate, Stanley, J. chem. Soc. 129: 89-101, 1926.
- <sup>15</sup> Chen, K. K., Steldt, Frank A., Fried, Joseph, and Elderfield, Robert C., J. pharm. and exp. therap. 74: 381-91, 1942.
- <sup>16</sup> Chiray, M. and Cuny, L., J. de pharm. et chimie (8), 9: 202-15, and 250-60, 1929.
- <sup>18</sup> Codex Medicamentarius gallicus—6 makol. 88: 113-57, 1920.
- <sup>13</sup> Codex Medicamentarius gallocus—6 ed. 1937, tome II-274-5.
- <sup>19</sup> Elderfield, Robert C., and Jacobs, Walter A., J. Biol. Chem. 107: 143-54, 1934.
- <sup>20</sup> Gilman, Henry, edit.: Organic Chemistry, an advanced treatise, Vol. II, 1333, N. Y. Wiley, 1938.
- <sup>21</sup> Gold, Harry, Cattell, McKeen, Kwit, Nathaniel T., and Kramer, Milton, J. pharmacol. and exp. therap. 72: 17, 1941.
- <sup>22</sup> Raymond-Hamet, Progress Medical, May 6, 1933: 817-27.
- <sup>23</sup> Raymond-Hamet, Progress Medical, June 3, 1933: 1006-19.

- <sup>24</sup> Homolle, M., *J. de pharm. et chimie*, (3), 7: 57-83, 1845.
- <sup>25</sup> Hudson, C.S. *J. Am. Chem. Soc.* 32: 338-346, 1910.
- <sup>26</sup> Jacobs, Walter A., *Physiol. Rev.* 13: 222-45, 1933.
- <sup>27</sup> Jacobs, Walter A., and Collins, Arnold M., *J. Biol. Chem.* 61: 387-403, 1924.
- <sup>28</sup> Jacobs, Walter A., and Elderfield, Robert C., *J. Biol. Chem.* 113: 611, 1936.
- <sup>29</sup> Jacobs, Walter A., and Elderfield, Robert C., *Science*, 80: 434, 1934.
- <sup>30</sup> Jacobs, Walter A., and Elderfield, Robert C., *J. Biol. Chem.* 114: 597-99, 1936.
- <sup>31</sup> Jacobs, Walter A., and Gustus, Edwin L., *J. Biol. Chem.*, 86: 199-216, 1930.
- <sup>32</sup> Jacobs, Walter A., and Gustus, Edwin L., *J. Biol. Chem.*, 74: 811-27, 1927.
- <sup>33</sup> Jacobs, Walter A., Hoffman, Alexander, and Gustus, Edwin L., *J. Biol. Chem.* 70: 1-11, 1926.
- <sup>34</sup> Jacobs, Walter A., and Hoffman, Alexander, *J. Biol. Chem.*, 67: 333-9, 1926.
- <sup>35</sup> Jacobs, Walter A., and Hoffman, Alexander, *J. Biol. Chem.*, 74: 787-94, 1927.
- <sup>36</sup> Kiliani, H., *Ber.* 25: 2116-18, 1892.
- <sup>37</sup> Kiliani H., *Pharm. J.*, (3), 22: 1061-64, 1892.
- <sup>38</sup> Kiliani, H., *Pharm. J.*, (4), 1: 29-31, 1895.
- <sup>39</sup> Kiliani, H., *Arch. pharm.* 233: 311-20, 1895.
- <sup>40</sup> Kiliani, H., and Merk, B., *Ber.* 34: 3564-77, 1901.
- <sup>41</sup> Kiliani, H., *Ber.* 43: 3562-74, 1910.
- <sup>42</sup> Kiliani, H., *Ber.* 49: 701-21, 1916.
- <sup>43</sup> Kiliani, H., *Ber.* 55B: 75-101, 1922.
- <sup>44</sup> Kon, G.A.R. *J. Soc. Chem. Ind.* 12: 593-95, 1934.
- <sup>45</sup> Kussner, W., *Arch. pharm.* 279: 41, 1941.
- <sup>46</sup> Lafon, cf. Vibert, Ch., *Précis de Toxicologie*, p. 482, Bailliere ed. Paris 1900.
- <sup>47</sup> Lamb, I.D., and Smith, S., *J. Chem. Soc.* 1: 442-7, 1936.
- <sup>48</sup> Leger, E. *J. de pharm. et chimie*, 18: 482-502, 1933.
- <sup>49</sup> Lettre, Hans, and Inhoffen, H. H.: *Die Saponine* Springer, ed. Vienna, 1927 (2nd. ed.).
- <sup>50</sup> Leulieu, Albert, and Griffon, Henri, *Bull. Sci. pharmacol.*, 36: 408-14, 1929.
- <sup>51</sup> Levene, P. A., and Compton, Jack, *J. Biol. Chem.* 111: 335-46, 1935.
- <sup>52</sup> Levene, P. A. and London, E. S. *J. Biol. Chem.* 81: 711-12, 1929.
- <sup>53</sup> Levene, P. A. and London, E. S., *J. Biol. Chem.* 83: 793-802, 1929.
- <sup>54</sup> Linville, Robert G., and Elderfield, Robert C., *J. Org. Chem.* 6: 270-72, 1941.
- <sup>55</sup> McPhillamy, Harold B., and Elderfield, Robert C., *J. Org. Chem.* 4: 150-61, 1939.
- <sup>56</sup> Mannich, C., *Pharm. zent.* 71: 615, 1930.
- <sup>57</sup> Marker, Russell E., Turner, D. L. and Ulshafer, Paul R., *J. Am. Chem. Soc.* 64: 1843-47, 1942.
- <sup>58</sup> Mendez, R., Krayner, O., Moisset de Espanes, E. and Linstead, R.P., *J. pharm. and exp. therap.* 74: 372-80, 1942.
- <sup>59</sup> Meyer, Hans, *Analyse und Konstitutionsermittlung organischer Verbindungen*, 6th Ed. Springer, Berlin, 1938.
- <sup>60</sup> Michael, Fritz, *Ber.*, 63: 347-59, 1930.
- <sup>61</sup> Moore, C. W., *J. Chem. Soc.* 95: 734-51, 1909.
- <sup>62</sup> Morel, A., and Marthoud, R., *Lyon pharmaceutica* 11: 70-193. (1935).
- <sup>63</sup> Nativelle, C.A., *J. de pharm. et chimie*, (4), 20: 81-7, 1874.
- <sup>64</sup> Paist, Walter D., Blout, Elkan R., Uhle, Frederick C., and Elderfield, Robert C., *J. Org. Chem.* 6: 273-88, 1941.
- <sup>65</sup> Perrot, E., *Progrès Medical*, Feb. 25, 1933 p. 354-57.
- <sup>66</sup> Perrot E. and Bourget, C. R. *Ac. Sc.* 186: 1021, 1928.
- <sup>67</sup> Rojahn, C. A., and Struffmann, F., *Pharm. Zent.* 70: 325-32, 341-46, 405-9, 1929.
- <sup>68</sup> Rubin, Martin, Paist, Walter D., and Elderfield, Robert C., *J. Org. Chem.* 6: 260-69, 1941.
- <sup>69</sup> Scagliola, Iside, *Giorn. farm. chim.* 76: 197-201, 1927.
- <sup>70</sup> Schmidt, Otto T., and Zeiser, Hans, *Ber.* 67B: 2127-31, 1934.
- <sup>71</sup> Schmiedeberg, Oswald, *Arch. f. exp. pathol. u pharm.* 3: 16-43, 1874.
- <sup>72</sup> Shoppee, C. W., and Reichstein, T., *Helv. Chem. Acta*, 23: 975-91, 1940.

<sup>73</sup> Sieve, Benjamin F., *Med. Ann.*, District of Columbia, 11: 47-51, 1942.

<sup>74</sup> Smith, S., *J. Chem. Soc.*, 133: 508-10, 1930.

<sup>75</sup> Stoll, Arthur, *The cardiac glucosides*, Pharm. Press, London, 1937.

<sup>76</sup> Stoll, Arthur, *J. Am. pharm. Ass.*, 27: 761-76, 1938.

<sup>77</sup> Stoll, Arthur U. S. Patent No. 2179204, 1940.

<sup>78</sup> Stoll, Arthur, Hoffman, A., and Kreis, W., *Z. physiol. Chem.*, 235: 249-64, 1935.

<sup>79</sup> Tambach, R., *Pharm. Zent.*, 53: 392-93, 1912.

<sup>80</sup> Tanret, M.C., *Bull. Soc. Chimie*, 15: 195-205, 1896.

<sup>81</sup> Tanret, M.C., *J. de pharm. et chimie*, (4), 22: 303-305, 1875.

<sup>82</sup> Tanret, M.C., *J. de pharm. et chimie*, (4), 22: 368-70, 1875.

<sup>83</sup> Thiele, Johannes, *Ann.* 319: 144-55, 1901.

<sup>84</sup> Torrey, John van P., Kuck, J. A., and Elderfield, Robert C., *J. Org. Chem.*, 6: 289-95, 1941.

<sup>85</sup> Wieland, Heinrich, Schlichting, Otto and Jacobi, Richard, *Zeit. physiol. Chem.* 161: 80-115, 1926.

<sup>86</sup> Windaus, A., and Hermans, L., *Ber.*, 48: 991-94, 1915.

<sup>87</sup> Windaus, A., and Schneckenburger, A., *Ber.*, 46: 2628-33, 1913.

<sup>88</sup> Windaus, A., and Shah, S.V., *Z. physiol. Chem.*, 151: 86-97, 1926.

<sup>89</sup> Wood, George B., and Bache, Franklin: *The dispensatory of The United States of America*, 14th edition, Lippincott, Philadelphia, 1877, p. 1141-45.

<sup>90</sup> Young, Frank G., Jr., and Elderfield, Robert C., *J. Org. Chem.* 7: 241-50, 1942.

## DIGITALIS GLUCOSIDE TESTS

See Baljet.

## DIGITALOSE

See Digitalis.

## DIGITIN

See Digitalis.

## DIGITIC ACID

See Digitalis.

## DIGITINE

See Digitalis.

## DIGITOGENIC ACID

See Digitalis.

## DIGITOGENIN

See Digitalis.

## DIGITONIN

See Digitalis.

## DIGITOXIGENIN

See Digitalis.

## DIGITOXIN

See Digitalis.

## DIGITOXOSE

See Digitalis.

## DIGITSAPONIN

See Digitalis.

## DIGOXIGENIN

See Digitalis.

## DIGOXIN

See Digitalis.

## DIHYDROCARVEOL

A terpene alcohol of caraway oil.

## DIHYDROCARVONE

A terpene ketone of caraway oil.

## DIHYDROCOENZYME I

Reduced coenzyme I

## DIHYDROCOENZYME I

## OXIDASE

See Xanthine Oxidase.

## DIHYDROEQUILENIN TEST

See Marx-Sobotka.

## DIHYDROXYACETONE

m.p. 80° C., obtained in fermentations and in carbohydrate metabolism, as in the action of acetic acid bacteria on glycerol.

## DIHYDROXYACETONE TEST

See Denigès.

See Campbell.

## DIHYDROXYHEXAHYDRO-CHRYSENE

See Estrogens, Synthetic.

**DIHYDROXYMALEIC  
OXIDASE**

A widely distributed enzyme of plant tissues which promotes the oxidation of dihydroxymaleic acid to diketosuccinic acid.

**o-DIHYDROXYPHENOLS,  
TEST FOR**

See Quastel, Denigès.

**DIHYDROXYSUCCINIC ACID**

See Tartaric acid.

**3:5-DIIODOTYROSINE**

Iodogorgoic acid, m.p. 198°, found in corals, sponges, thyroid glands, and may be a precursor or component of the thyroid hormone.

**DIKETOPIPERAZINES**

The cyclic anhydrides of two amino acids. In the American classification of proteins, they are classified as secondary protein derivatives.

**DIKETOPIPERAZINE TEST**

See Sasaki.

**DILAUDID**

Dihydromorphinone hydrochloride, a synthetic made from morphine in order to cut down its harmful features.

**DILLE-KOPANYI TEST FOR  
BARBITURIC ACID  
DERIVATIVES**

The aqueous solution of the substance (acidified with hydrochloric acid if necessary) is extracted with chloroform; 2 parts of the chloroform extract are treated with 0.1 part of a 1% solution of cobalt acetate in absolute methanol and 0.6 parts of isopropylamine in methanol. A red-violet color indicates a positive test which can be used quantitatively.

Reference: J. Am. Pharm. Assoc. 23, 1079 (1934).

**DIMETHYLMORPHINE**

See Thebaine.

**DIMYRISTYL CARBINOL**

A constituent of apple cuticle.

**2, 4-DINITROPHENOL**

A compound which on ingestion raises the basal metabolism to a marked degree.

**DIONINE**

Ethyl morphine, a synthetic.

**DIOSCORINE**

An alkaloid,  $C_{13}H_{19}O_2N$ , from the tubers of *Dioscorea hirsuta*, which is toxic, acting like picrotoxin.

**DIOSES**

Monosaccharides with the formula  $C_2H_4O_2$ .

**DIOSMIN**

See Flavone Glycosides.

**DIPEPTIDASE**

A proteolytic enzyme that hydrolyzes dipeptides only when there is a hydrogen alpha to an amino group, one alpha to a carboxyl group, and one alpha to the peptide nitrogen.

See also Autolysis.

**DIPEPTIDE**

A polypeptide containing two amino acids.

**DIPHENYL DERIVATIVES,  
ESTROGENIC ACTIVITY OF**

See Estrogens, Synthetic.

**DIPHENYL ETHANE  
DERIVATIVES, ESTROGENIC  
ACTIVITIES OF**

See Estrogens, Synthetic.

**DIPHENYL METHANE  
DERIVATIVES, ESTROGENIC  
ACTIVITY OF**

See Estrogens, Synthetic.

**DIPHThERIA**

A contagious disease caused by the Klebs-Löffler bacillus, characterized by the formation of false

membranes on mucosae of the upper respiratory tract or the skin and a toxemia highly injurious to peripheral nerves and the heart. The Schick test for immunity by the injection of diphtheria toxin to produce an inflammatory reaction of the skin, may be of diagnostic aid. Varieties of diphtheria are pharyngeal, nasal, laryngeal (true membranous croup), malignant diphtheria and diphtheria of various parts as the skin, genitalia, etc. There is great danger of complications, such as albuminuria, pneumonia, myocarditis, otitis media, neuropathy, secondary anemia. Various types of immunization have been developed as toxin-antitoxin, formalized toxoid, alum precipitated toxoid. The treatment leans heavily on antitoxin administration. Recovered patients frequently remain carriers of the organism.

#### DIPHTHERIA IMMUNITY TEST

See Schick.

#### DIPLOID

Pertaining to cells having a full number of chromosomes, twice the number that a gamete has, e.g. somatic cells.

#### DIPNEUST, DIPNOI

Fishes that breathe both by gills and lungs.

#### DIPOLE ION

See Zwitterion.

#### DISACCHARIDASES

See Enzymes, Non-Proteolytic.

#### DISACCHARIDE

The sugar resulting from the condensation of two molecules of a monosaccharide, with the loss of water. Reducing disaccharides reduce Fehling's solution, due to

a functional or potentially functional aldehyde group, non-reducing do not.

#### DISACCHARIDES

##### I. Reducing Disaccharides:

Cellobiose is glucopyranose-4- $\beta$ -glucopyranoside.

Gentiobiose is glucopyranose-6- $\beta$ -glucopyranoside.

Isolactose is a glucose galactoside.

Lactose is glucopyranose-4- $\beta$ -galactopyranoside.

Maltose is glucopyranose-4- $\alpha$ -glucopyranoside.

Melibiose is glucopyranose-6- $\alpha$ -galactopyranoside.

Turanose is  $\beta$ -fructofuranose-6- $\alpha$ -glucopyranoside.

##### II. Non-reducing Disaccharides:

Isotrehalose is  $\beta$ -glucose- $\beta$ -glucoside.

Sucrose is  $\alpha$ -glucopyranose-1- $\beta$ -fructofuranoside.

Trehalose is  $\alpha$ -glucopyranose-1- $\alpha$ -glucopyranoside.

#### DISMUTATIONS

(1) Coenzyme-linked reactions in which the same compound is both reductant and oxidant for the coenzyme, e.g. the formation of phosphoglycerate and alpha-glycerophosphate from 2 molecules of triosephosphate in muscle glycolysis with the intermediation of Coenzyme I;

(2) In general, simultaneous oxidation and reduction, as in the Cannizzaro reaction.

#### DISPERMIN

See Piperazine.

#### DISPERSION

Any mixture where one substance is very intimately intermingled with another. Most frequently a dispersion refers to a colloidal suspension.

**DISSIMILATION**

See Microbiology.

**DISSOCIATING PROTEIDS**

Enzymes which are conjugated proteins which contain a prosthetic group.

**DISSOCIATION CONSTANT**

For a dissociated compound at equilibrium, the product of the concentration of anion by the concentration of cation, divided by the concentration of undissociated compound, is a constant for a definite temperature. This is called the dissociation constant, or ionization constant.

**DITAINÉ**

See Echitamine.

**DITHIAMINE**

See Cocarboxylase.

**DIURETIC**

Promoting the secretion of urine.

**DIVERSINE**

$C_{16}H_{18}(NCH_3)(OCH_3)_2(OH)_2CO$ ; alkaloid; m.p. 80-93°; increases reflexes; vasoconstrictor; paralyzes peripheral motor nerve apparatus; lethal action through respiratory paralysis.

**DIVERTICULUS**

See Gastro-Enterology.

**DJENKOLIC ACID**

A sulfur containing dicarboxylic amino acid of velvet beans, possibly a minor constituent of other proteins.

**D:N RATIO**

See Blood Sugar.

**DOCA**

A commercial preparation of synthetic desoxycorticosterone acetate.

**DOMINIKIEWCZ TEST FOR REDUCING SUGARS**

The addition of 3,6-dinitro-2,7-di-

hydroxyfluoran to an alkaline solution of a reducing sugar gives rise to a cerise color which changes, on acidification, to an intense orange fluorescence. Sensitivity—0.013 mg. per cc.

Reference: *Roczniki Chem.* 12, 686 (1932).

**DONNAN EQUILIBRIUM**

If an aqueous solution of NaR (I) is separated from an aqueous solution of NaCl (II) by a membrane permeable to all ions except R<sup>-</sup>, then diffusion of Cl<sup>-</sup> ions to (I) will take place. At equilibrium the product of the concentration of the diffusible ions (Na<sup>+</sup>) (Cl<sup>-</sup>) on one side of the membrane will be equal to the product of (Na<sup>+</sup>) (Cl<sup>-</sup>) on the other side. Due to the fact that the concentration of Na<sup>+</sup> on the side containing the non-diffusible R<sup>-</sup> is greater than the concentration of Cl<sup>-</sup>, a potential difference is set up across the membrane.

**DONOGANY TEST FOR BLOOD**

The addition of 1 cc. ammonium sulfide and 1 cc. pyridine to 10 cc. of urine produces an orange-red mixture showing a characteristic absorption spectrum.

The test material may be extracted with 20% sodium hydroxide and 1 drop of extract mixed with 1 drop of pyridine on a slide. Characteristic crystals of hemochromogen form after a few hours; i.e. orange-yellow to brownish needles in star-like arrangements.

Reference: *Arch. path. Anat.* (Virchow's) 148, 234 (1897). *Deut. Med. Wochschr.* 1909, 1191. *Vierteljahresschr. gerichtl. Med.* 307, II, Suppl. 27. *Münch. med. Wochschr.* 1910, 1086.

**DOPA**

3:4-dihydroxyphenylalanine, m.p. 282°, an amino acid of plant origin,



also formed from tyrosine as it oxidizes to melanin.

See also Bloch Dopa Reaction.

# DOPA REACTION

See Bloch.

# DORN EFFECT

See Streaming Potential.

# DOVER'S POWDER

A powder of 10% each of ipecac and opium and 80% lactose; sedative, anodyne, diaphoretic.

# DOWN

See Hair.

# DPN

Diphosphopyridinenucleotide or cozymase.

# DRECHSEL TEST FOR BILE ACIDS

This is a modification of the Pettenkofer test wherein syrupy phosphoric acid is used in place of sulfuric acid.

Reference: J. prakt. Chem. 24, 44 (1891); 27, 424 (1883).

# DRUGS

See Pharmacology.

# DRYING OIL

A comparatively highly unsaturated oil which absorbs oxygen to become a stable, insoluble solid film. Linseed oil is largely used in the paint industry because of this property.

# DUBSKY-HRDLÍKA MICROREAGENT FOR ALUMINUM

A red, non-specific lake is obtained by the interaction of aluminum with the potassium salt of 1-aminoanthraquinone-2-carboxylic acid. Sensitivity — 1:220000. Magnesium and zinc give less sensitive tests.

Reference: Mikrochemie 22, 116 (1937).

# DUCLAUX SYSTEM

See Enzymes, Non-Proteolytic.

# DULCIN

p-phenetolcarbamide; about 250 times as sweet as cane sugar.

# DULCITOL

The hexahydroxyhexane derived from galactose; m.p. 188° C.; optically inactive (meso).

# DUODENIN

See Secretin.

# DUODENUM

See Gastro-Enterology.

# DUPPA-PERKIN REACTION FOR GLYOXYLIC ACID

I. The filtrate obtained after the precipitation of calcium oxalate from calcium glyoxalate, by aniline oxalate, forms a light orange-yellow precipitate on long standing.

II. When a glyoxylic acid solution is boiled with lime, oxalic acid is split off.

Reference: Ber. 19, 595 (1886).

# DURUMIN

The prolamine of durum wheat.

# DYER-BAUDISCH REACTION FOR CYSTEINE AND CYSTINE

The reagent (o-benzoquinone) is prepared by shaking a mixture of 1.5 gm. silver oxide, 1.5 gm. anhydrous cadmium sulfate and 0.4 gm. catechol with 10 cc. of anhydrous ether for 35 seconds. After rapid filtration, the filtrate is placed in a freezing mixture. The ether is decanted, and the crystals are immediately washed with 1-2 cc. of ether and dissolved with 8 cc. chloroform.

2 cc. of reagent are added to 2 cc. of sample and shaken vigorously for 2 minutes; a deep red color appears in the chloroform.

1 cc. hydrochloric acid and a few fragments of mossy tin are added

to 1 cc. cystine solution and heated for 2 minutes. The solution is filtered, diluted with water to 15 cc. and saturated with hydrogen sulfide. 0.2 gm. charcoal are added, Shake for 1 minute and filter. Hydrogen sulfide is expelled by boiling, the solution cooled, acidified, treated with 4 cc. of reagent and shaken, giving a deep red color.

Reference: J. Biol. Chem. 93, 483 (1932).

### DYNAMIC BIOCHEMISTRY

See Biochemistry (Definitions).

### DYNAMIC EQUILIBRIUM

See Steady State.

### DYSLYSINE

$C_{24}H_{38}O_3$ , a reduction product of cholic acid by bacteria, found in feces.

### DYSMENORRHEA

Painful menstruation, caused principally by excessive tension or contraction of the uterus, or by ischemia (high intrauterine pressure). These are a sign of endocrine dysfunction or structural faults or faulty sex hygiene. Primary or essential dysmenorrhea is accompanied by pain only at menstrual periods. Palliatives are various analgesics and antispasmodics. Hormone therapy is adapted either to hypoovarianism or hypothyroidism as diagnosed. Progesterone is frequently administered. Intermenstrual pain

may require surgical treatment or X-ray castration.

See also Estrogens, Synthetic.

### DYSPNEA

A condition where there is the awareness of a need of increased respiration which may be accompanied by cyanosis, a dark-bluish discoloration of the mucous membranes or the skin on account of decreased oxygen content of the blood and a simultaneous increase in carbon dioxide. Various types accompanied by cyanosis have been described, e.g. pulmonary dyspnea, cardiac dyspnea. Dyspnea without cyanosis occurs in acidosis such as due to ketosis or uremia, centric irritability (of the respiratory center). It may be hemic, i.e. due to faulty blood supply of the respiratory center, or even psychic, i.e. due to hysteria. Cyanosis without dyspnea is found in heart disease, narcotic poisoning (as in advanced stages of alcoholism, overdoses of morphine, hypnotics, etc.) and as a terminal phenomenon. Treatments are causal and involve removal of obstruction, promotion of circulation, vasodilation, diuresis, oxygen inhalations, and judicious use of both stimulants and sedatives.

### DYSTROPHY

Inadequate nutrition.

### DYSTROPHY, MUSCULAR

See Creatine and Creatinine Metabolism.

## E

### 1-ECGONINE

$C_9H_{15}O_3NH_{20}$ ; tropine-2-carboxylic acid; monoclinic prisms from alcohol, m.p.  $198^\circ$  (dec.); an alkaloid of *Erythroxylon Coca*. It is the starting material for synthetic cocaine.

### ECHINODERMATA

A class including: astroidea—starfishes; holothuroidea—sea cucumbers; echinoidea—sea urchins.

### ECHITAMINE

Ditaine, an alkaloid,  $C_{22}H_{28}O_4N_2 \cdot H_2O$ ; m.p.  $206^\circ$ ; from bark of *Alstonia scholaris*; used as febrifuge or tonic in chronic diarrhea and advanced stages of dysentery.

### ECLAMPSIA

Puerperal convulsions; a toxic condition of pregnancy brought on by metabolic disturbances or death of the foetus. There is a rise in blood pressure, albuminuria, increased non-protein nitrogen and other signs of kidney insufficiency. Treatments are directed toward the control of convulsions, e.g. by morphine and chloral, and relief of hypertension, e.g. by venesection.

### ECOLOGY

The study of the relations of organisms to their environment.

### ECTODERM

External cellular layer of the em-

bryo, forming the outer covering and nervous system, and originating largely from the animal pole of the egg.

### ECTOPLASM

The outer, stiffer portion or region of the cytoplasm of a cell which may be differentiated in texture from the inner portion or endoplasm.

### ECZEMA

An exudative skin inflammation which may be acute, subacute or chronic, produced by various exciting factors which may be chemical, mechanical, thermal, radiant (sun's rays), allergic, or endocrine. The following types are described: (1) erythema, (2) papules, (3) vesicles, (4) pustules, (5) weeping eczema, (6) rubrum (red), (7) squamosum (scaly), (8) fissum (fissures or chapping), (9) sclerosum (chronic, leathery) and (10) verrucosum (wart-like).

Rational treatment requires removal of cause, powdering as with zinc stearate, applying zinc pastes or boric acid lotions or starch poultices. Roentgen rays, ultraviolet rays and radium are used for obstinate chronic cases. There is also some basis for "alkalizing" and calcium therapy. Aller-

gy must be ruled out. Special techniques are used for children's types called collectively "infantile eczema."

See also Itching.

#### EDELMANN TEST FOR UROBILIN IN URINE

10 cc. of urine are mixed with 5 cc. reagent A (10% alcoholic mercuric chloride solution) and extracted with amyl alcohol. The clear alcohol extract is treated with some reagent B (10% alcoholic zinc chloride solution); a rose-red color is obtained and further addition of zinc chloride produces a fluorescence.

Reference: Wiener klin. Wochschr. 1915, 978. Deut. med. Wochschr. 1915, 1287.

#### EDEMA OF THE LUNGS

Acute pulmonary edema; may also be chronic; a condition of accumulation of serum from the capillaries into the lung tissue or the alveoli and the bronchi. It may be provoked by poisons, inflammatory processes or abnormal osmotic relations provoked by disturbance of plasma constituents, as proteins, salts, lipoids, and sheer damages to capillary walls, as in pneumonia. Morphine, diuretics (theophylline), venesection, and oxygen administration are used to break up a vicious circle in which dyspnea sets in and further aggravates the edema. One tries to prevent death by drowning, so to speak.

#### EDESTIN

A globulin from hemp seed containing all the amino acids essential for a complete protein supply, m.w. 309,000.

#### EDESTIN TEST

A test for gastric cancer based

on the prescence of a peptide splitting ferment.

#### EEGRIWE TEST FOR GLYCERIC ACID

A few cc. of an 0.01% solution of naphthoresorcinol in sulfuric acid are added to a drop of the test solution and heated at 90° for 30-50 minutes. Dependent upon the concentration of glyceric acid, a light to dark blue color is obtained. Sensitivity—0.05 mg.

Reference: Zeit. anal. Chem. 95, 323 (1933).

#### EEGRIWE TEST FOR GLYCOLIC ACID

A small amount of substance is heated with a sulfuric acid solution of 2,7-dihydroxynaphthalene; a violet-red color is obtained.

Reference: J. pharm. chim. 1933, 161. Zeit. anal. Chem. 89, 121 (1932).

#### EEGRIWE TEST FOR LACTIC ACID

A drop of test solution is heated at 85° with 1 cc. sulfuric acid for a minute, cooled to 25° and treated with a little solid p-hydroxydiphenyl. After 30 minutes, a violet color is obtained. Sensitivity—0.1 mg.

Reference: Zeit. anal. Chem. 95, 323 (1933); 100, 31 (1935).

#### EFFECTORS

See Nervous System.

#### EFFICIENCY OF FOOD UTILIZATION

This is the quotient: Change in desired effect of food divided by corresponding change in food intake.

M. K.

#### EFFICIENCY OF FOOD UTILIZATION, MEAN PARTIAL

This is the quotient: (Desired effect of food plus prevention of

loss which would occur without food divided by total food intake.

M. K.

### EFFICIENCY OF FOOD UTILIZATION, TOTAL

Quotient: desired effect of food divided by total food intake. Examples: gain in bodyweight per pound of food consumed. Calories of energy in milk per calory—or per 100 calories — of food energy consumed.

M. K.

### EHRlich's DIAZO REAGENT

See van den Bergh Test.

### EHRlich-KOZLEZKOWSKY SOLUTION

See Kahn Test for Arsphenamine Injuries.

### EHRlich TEST FOR BILE PIGMENTS IN URINE

The urine is extracted with chloroform and treated with equal volumes of Ehrlich's diazo reagent and concentrated hydrochloric acid; a violet color, changing to blue-violet and finally to blue is obtained.

Reference: Zeit. anal. Chem. 23, 275 (1884); 39, 735 (1900). Wiener klin. Wochschr. 1898, No. 8. Petersburger med. Wochschr. 1905, 128. Canada. Med. Assoc. 23, 823 (1930).

### EHRlich TEST FOR INDICAN IN URINE

1-1.5 cc. of urine are boiled with an equal volume of reagent (0.33 gm. p-dimethylaminobenzaldehyde in 50 cc. water and 50 cc. concentrated hydrochloric acid), cooled and treated with excess ammonia or dilute sodium hydroxide. The intensity of the red color produced may be used to estimate the quantity of indican.

Reference: Pharm. Zentralhalle

1905, 89, 1911, 382. Münch. med. Wochschr. 1910, 654. Compt. rend. 147,214 (1908). Med. klin. 1913, 294.

### EHRlich's REAGENT

p-dimethylamino benzaldehyde, used as a specific test for indole derivatives, and therefore for proteins containing the indole nucleus. The material to be tested is treated with 20% HCl and Ehrlich's reagent (or benzaldehyde). An intense blue color is positive.

### EKKERT REACTIONS FOR ADRENALINE AND EPHEDRINE

When treated with anisaldehyde and sulfanilic acid, adrenaline and ephedrine give bright violet-rose colors; adrenaline gives a yellow to flesh color and ephedrine a dichromate red with salicylaldehyde and sulfuric acid. Adrenaline, with sulfanilic acid, 5N hydrochloric acid and 0.7% sodium nitrite solution forms deep rose-red rapidly; ephedrine takes longer. With 10% potassium hydroxide solution, adrenaline forms an evanescent red color and after evaporation a gray residue with greenish cast; ephedrine gives no color but forms an orange to dichromate red residue on evaporation.

Reference: Pharm. Zentralhalle 75, 208 (1934).

### ELAEOSTEARIC ACID

An 18 carbon unsaturated fatty acid with two double bonds, found in Japanese wood oil.

### ELAIDIC ACID.

An unsaturated fatty acid,  $C_{18}H_{34}O_2$ , an isomer of oleic acid, which does not occur naturally; m.p. 51-2° C.

### ELASMOBRANCH

Fish of shark type.

**ELASTICITY, PROTOPLASMIC**

See Protoplasm.

**ELASTIN**

A scleroprotein found in connective tissue, tendons, cartilage and particularly in the respiratory system. It is insoluble in water, dilute acids and alkalies and salt solutions. It is more readily hydrolyzed by trypsin than by pepsin. It has a high content of glycine and leucine.

**ELATERIUM**

A product of the juice of the squirting cucumber containing "elaterin" a most powerful water producing purgative, used to relieve dropsy.

**ELDRIN**

See Rutin.

**ELECTRICAL FORCES, LIFE**

See Protoplasm.

**ELECTRICAL PRECIPITATION**

See Cottrell Precipitation.

**ELECTRIC SHOCK IN MENTAL DISEASE**

See Psychiatry, Biochemistry of.

**ELECTRODE POTENTIAL**

The potential developed on an inert metal, such as platinum, when it is inserted in a reversible oxidation-reduction system, or a concentration half-cell, and connected to some other half-cell, such as a calomel half-cell.

**ELECTROENDOSMOSIS**

The passage of liquid through a membrane or colloidal gel under the force of an applied electric current.

See Protoplasm.

**ELECTRODIALYSIS**

A more rapid form of dialysis, which takes advantage of the fact that electrolytes are charged particles, and move more rapidly under

the influence of a direct electric current to the anode and cathode. The colloidal sol is restrained by suitable membranes from moving to the anode or cathode.

**ELECTROKINETICS**

The study of motion set up by an applied electromotive force, and of the production of an e.m.f. by motion such as the flow of liquids.

**ELECTROLYTE**

An acid, base, or salt, which when dissolved in water, dissociates into electrically charged particles called ions. The solution can conduct an electric current.

**ELECTROLYTE BALANCE IN MUSCLE**

The facts of electrolyte balance particularly in muscle cells are admirably reviewed in the articles of Fenn (1936) and Steinbach (1940). There are several striking facts the explanations of which have given rise to much speculation. An examination of the total osmotically active constituents reveals that there exists a large excess of cation equivalents over anion equivalents in the cells of muscles. In a total of 130 there are missing 47 mille equivalents of anions per kilo of muscle. Using Weber's (1934) data on muscle proteins, with a generous allowance only 26 mille equivalents (meq.) of base can be thus accounted for. This is probably an overestimation, for Fenn and Maurer (1935) have estimated the pH inside the fibers to be at 6.9. Their method depending on CO<sub>2</sub> combination at different carbon dioxide tensions and the use of the Henderson-Hasselbach equation, would tend to make the pH too high rather than too low. This necessarily removes much of the protein for use as base equivalents.



Undoubtedly part of this question of anion deficit is tied up with the problem of the phosphate fraction. The data of both Fenn (1936) and Eggleton (1935) agree in putting the total phosphate at about 33 millimols per kilo of fresh tissue. However at least one investigator, Netter (1934), puts the acid soluble phosphate at 50 millimols per kilo. In any case the extreme lability of phosphate, especially in muscle makes a decision as to its equivalent value difficult.

The fact that there is at least an apparent anion deficit has given rise to the notion that the cells of muscle (and other tissues as well) are surrounded by a membrane impermeable to anions. In connection with this, mention must be made of the chloride problem. For a long time the belief has been held that cells are impermeable to chloride, one of the commonest ions in the cellular environment. The evidence for this assumption has been entirely indirect due mainly to the difficulty of a direct attack on the problem. One great experimental embarrassment encountered in the study of muscle electrolytes and chloride in particular is the presence of tissue spaces, and the consequent necessity for estimating electrolytes present in the interstitial fluid. Direct measurements of this interstitial space in frozen sections of frog sartorius has yielded 14.5% and 17.5% of total volume in two attempts made by Hermann (1888) and Fenn (1936) respectively. Schulze's (1927) data for frog muscle, obtained by an electrical method, when correctly calculated, yields a value of 13.9% rather than the 36% he reported. Since all the evidence indicates that the perimysium of muscle is perfectly perme-

able to electrolytes the interstitial fluid must be in simple equilibrium with the immediate environment, as far as these components are concerned. Consequently since the approximately 15% of extracellular space is also included, the presence of a particular ion in an analysis of a whole muscle does not necessarily imply that it can penetrate into the cells. It was naturally not surprising to find chloride in whole muscle. However, Fenn et. al (1934) have shown for frog sartorius and gastrocnemius that if all the chloride were confined to 14.7% of the total muscle volume it would have a concentration equal to the chloride content of frog blood plasma. The close agreement between this chloride value and that obtained by histological and electrical measurements for the interstitial space would seem to suggest that all of the chloride is extracellular. This has given rise to the concept, almost universally adopted in physiological literature that chloride space and intercellular space are identical. By using this chloride space and assuming simple equilibrium between interstitial fluid and the environment, one can subtract from an analysis the proportion of a particular ion which is extracellular and arrive at an estimate of its intracellular "concentration." This type of calculation has been used extensively in most of the papers on electrolyte balance. In addition to the fact that no direct evidence has been offered supporting the basic assumption of chloride impermeability the weight of recent evidence seems to deny its validity. The most convincing arguments against chloride impermeability of cells came first from experimenters who did not have to contend with the problem of extra cellular space.

Krogh (1938) has shown that with some types of eggs chloride can move back and forth with considerable ease. Bear and Schmitt (1939) in analyzing the giant axon of squid reported considerable amounts of chloride, about 20 per cent as much as sea water. Steinbach (1940) using the same material not only confirmed these findings but showed that he could move chloride across the cell boundary in either direction by suitable changes in the environment. However even in muscle physiology all authors have not been content to regard the muscle as devoid of chloride. Conway et al. (1939), after studying the diffusion of chloride from excised muscle concluded that some of the chloride which diffused out was originally contained within the fibers. Other authors who come to the same conclusion are Fisher and Subrahmanyam (1939), Boyle et al. (1941) and Boyle and Conway (1941). It was left to Heilbrunn and Hamilton (1942) to deliver what at the present reading appears to be the most telling blow against the chloride impermeability hypothesis. These investigators made a direct attack on the problem by dissecting out single muscle fibers for analysis and thus avoiding the interstitial volume complication. They found that the fibers contained about 80 per cent as much chloride as the whole muscle. This would come to 50 meq. per kilo and would wipe out the anion deficit and possibly create a cation one. Whatever the final decision will be it is becoming increasingly evident that muscle (as well as other cells) are not chloride impermeable but do possess a chloride depleting mechanism which is somehow tied up with metabolism for when a

cell dies along with other changes a chloride influx takes place.

Phosphate balance presents an absorbing problem whose importance is enhanced by the recent research emphasizing the role of phosphate metabolism in energy transfer. Aside from this, the story of the development of our knowledge of phosphate balance has a pointed lesson whose moral has for the most part been sadly missed.

The internal 'concentration' of phosphate is approximately 33 meq. per kilo of tissue. However the environment (plasma) of the same muscle contains only 3.1 meq. per kilo. It would appear then that cells 'concentrate' phosphate. Unfortunately phosphate is an anion and thus in the early literature fell into the class of 'impermeables' almost by definition. This impermeability of phosphate was held for a long time despite the high phosphate content of cells. Embden and Adler (1922) first observed the diffusion of phosphate from muscle. However their interpretation did not violate the 'anion impermeability law' drastically, only slightly. They postulated a 'temporary increased membrane permeability for phosphate.' Further work led to the discovery that more phosphate was lost during asphyxia or stimulation. With the advent of phosphocreatine and the clarification of its role in muscle chemistry several things became immediately evident. Previous methods of analysis involving as they did drastic acid hydrolysis did not distinguish between organic or bound phosphate and inorganic phosphate free to move under the influence of concentration gradients. The calculation of phosphate 'concentration' on the basis of these analyses was

clearly meaningless if the word concentration implies a given amount of solute dissolved in a solvent and free to obey the ordinary laws of diffusion. The whole problem was clarified when Eggleton (1929) showed that the diffusion of phosphate out of the cell was not proportional to total phosphate but to the amount of free phosphoric acid. It then became unnecessary to postulate 'temporary changes in membrane permeability' to explain the egress of phosphate during stimulation or asphyxia. On the contrary, with the assumption of complete membrane permeability accumulations of free phosphate during those conditions would explain satisfactorily the phenomena observed.

One other aspect of the problem was illuminated by these simple facts. It was of course hard for membrane theorists to explain how an anion could get into the cell in the first place, let alone move against a concentration gradient as it seemed to do part of the time when phosphate was being accumulated. It is clear now that the actual amount of free phosphate in the resting muscle is very small and that consequently a concentration gradient need not exist. Postulating the existence of selectively permeable or impermeable membranes as a mechanism for ionic concentration or accumulation becomes superfluous since a simple chemical combination within would appear to be adequate.

Precisely the same problems are met with when the balance of cations is considered. Large amounts of potassium are found in cells whereas comparatively small amounts exist in their environment. For sodium the reverse relation is obtained. Sodium is the commonest

cation in the environment but little is found in cells. Thus a condition similar to the phosphate-chloride story obtains here, inasmuch as the cells seem to select the less abundant ion. Again a selective membrane hypothesis was early postulated, the cell membrane being presumed to be permeable to potassium and impermeable to sodium. The physical basis of this selectivity was not examined and rarely referred to. However, close study reveals that much of the charm of this simple 'explanation' is illusory. Spiegelman and Reiner (1942) in a kinetic analysis of potassium accumulation and sodium exclusion have shown that selective membrane theories are committed to awkward assumptions about the potential distributions of these ions with reference to the cytoplasm, cell membrane and external environment. In the same paper they calculate the amount of energy necessary to concentrate potassium in the presence of sodium to the extent found in frog muscle and obtain a value of 10,000 calories per mole. An examination of the known physical forces which can be postulated for membranes preferentially accumulating potassium finds them entirely inadequate. Recently Boyle and Conway (1942) in an extensive paper have proposed a theory to explain electrolyte balance in muscle based on the primary assumptions of membrane impermeability to sodium and simple thermodynamic equilibrium with the environment. This paper has received wide attention because of its apparent success in explaining muscle volume changes under various environmental conditions. However it can be shown (Spiegelman, 1942, unpublished) that the deductions of these volume changes can be made independently of the Na

impermeability postulate. Furthermore recent years have seen the accumulation of many facts which directly question the validity of this assumption. A large number of workers have shown that sodium readily exchanges for potassium under certain conditions, (see Fenn, 1940). Two particularly significant contributions have recently been made which should settle the question. Steinbach (1940) using isolated resting frog muscle found that forty per cent of the potassium was replaced by sodium when it was soaked in potassium-free Ringer's. Returning the muscle to ordinary Ringer's resulted in a potassium reconcentration. Heppel (1939) showed that fully one half of the potassium in the intact muscles of rats could be replaced with sodium if they were raised on a potassium deficient diet. He (Heppel, 1940) further showed with the use of radioactive sodium that the penetration of sodium was if anything more rapid than that of potassium. Indeed calculations from his data would indicate that sodium penetrates into cells eight times faster than potassium. These as well as other experiments would indicate that the answer to potassium accumulation and sodium exclusion must be sought for inside the cell rather than in a mysteriously propertied membrane.

Dean (1941) in an attempt to avoid the impermeability postulate proposed a modification of the Conway and Boyle theory which assumed the existence of a 'sodium pump' which got rid of sodium as fast as it diffused in. An examination of his equations reveals that his primary assumption involves different partition coefficients between the cell and the environment

for potassium and sodium ions. The 'pump' mechanism is merely a verbalistic cloak for this relatively simple chemical assumption.

Some authors have preferred to depend on ionic mobility differences to explain preferential assimilation, assuming that since the potassium has a higher mobility it penetrates more easily. However it can be shown (Spiegelman and Reiner, 1942) that mobility differences per se cannot lead to selective accumulation of the faster ion.

Unfortunately the kind of solution for phosphate accumulation which appeared with the discovery of phosphocreatine is not yet available for the case of potassium. Thus far it is not possible to distinguish analytically between free and bound potassium or sodium. Until this distinction is possible it should be borne in mind that the concentrations of these ions obtained with available methods of analysis do not necessarily imply that the entire amount is free to diffuse. In connection with this, one suggestive experiment was briefly reported by Mullins (1942) who showed that suspensions of the protein myosin selectively adsorbed potassium from mixtures of that ion and sodium. This would offer a simple and forthright explanation for the potassium selectivity of muscle cells. More experiments are however required before a decision can be arrived at.

The continued emphasis on static membrane theories has led to a serious neglect of the connection between electrolytes and metabolic processes. The question of what potassium is doing inside the cell has been rarely asked or considered. The chief role thus far assigned to this ion has been as a balance for

the colloidal anions and to make up the osmotic pressure of the fibers. If this be the only function of potassium it is proper to ask why the more abundant sodium ion would not do just as well.

Some beginnings have however been made in this direction. A serious barrier to progress has been the conclusion by some authors that the gain or loss of potassium in muscle is independent of metabolism. This conclusion was based on the experiment which indicated that potassium can enter a cell against a concentration gradient just as well anaerobically as aerobically. It is patently apparent that this conclusion is unjustified, for it has been amply demonstrated that immediate sources of energy exist, other than aerobic oxidation. Consequently it does not follow that because a process can take place in the absence of oxygen it is 'non-metabolic.' (Many obligative anaerobic bacteria would be seriously embarrassed by this conclusion if they were to take it seriously.) In any case Fenn (1941) points out that while isolated frog muscle immersed in oxygen free solutions lost little more potassium than similar muscles in oxygen, the loss became appreciable when glycolysis was also prevented by iodoacetate poisoning. Furthermore data on electrolyte changes during muscular contraction (Fenn, 1940, 1941) furnish rather convincing evidence for some connection with the chemistry of contraction. Briefly, stimulation seems to be followed by loss of potassium and phosphate simultaneously accompanied with a gain of sodium and chloride.

As compared with such fields as plant physiology however, the problem of the relation between electro-

lytes and general metabolism in muscle is as yet in an embryonic condition. The existent literature does at least provide several interesting leads. The muscle is a mechanism whose function it is to contract. The weight of the evidence is in favor of myosin as the contractile element. What is the K-binding power of myosin in the contracted as compared with the relaxed state? What is the effect of different Na-K ratios on the contractility of myosin fibers? What is the effect of these ratios on its phosphatase activity? What groupings in the myosin molecule are responsible for its selective adsorption of potassium? The answers to these questions will provide at least part of the knowledge we would like to have about electrolyte balance and muscle physiology.

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#### BIBLIOGRAPHY

A brief bibliography from which may be obtained all the references mentioned in the discussion.

- Boyle, P. J. and Conway, E. J.: 1941, *Jour. Physiol.*, 100: 1.  
Dean, R. B.: 1941, *Biol. Symp.*, 3: 331.  
Fenn, W. O.: 1936, *Physiol. Rev.*, 16: 450.  
1940, *Physiol. Rev.*, 20: 377.  
1941, *Ann. Rev. Physiol.*, 3: 209.  
Heilbrunn, L. V. and Hamilton, P. G.: 1942, *Physiol. Zool.*, 15: 363.  
Heppel, L. A.: 1939, *Am. J. Physiol.*, 127: 385.  
1940, *Am. J. Physiol.*, 128: 440, 449.  
Mullins, L. J.: *Fed. Proceed.*, Part II, Vol. I: 61.  
Spiegelman, S. and Reiner, J. M.: 1942, *Growth* (in press).  
Steinbach, H. B.: 1940a, *Cold Spring Harbor Symp.*, 8: 242.  
1940b, *J. Biol. Chem.*, 133: 695.

#### ELECTROPHORESIS

The movement of solid particles through stationary liquids due to an imposed e.m.f.

**ELECTROPHORETIC BEHAVIOR (AND TAXONOMY)**

See Protoplasm.

**ELECTROTROPISM**

Reaction to the electric current.

**ELECTRO-ULTRAFILTRATION**

A more rapid method of ultrafiltration, and one which can be used at atmospheric pressures. It utilizes the fact that both electrolytes and water will pass through semi-permeable membranes more rapidly under the influence of a direct electric current.

**ELEPHANTIASIS GRAECORUM**

See Leprosy.

**ELLAGIC ACID**

A cyclic acid,  $C_{14}H_6O_8$ , from oak bark and galls, originating from tannin.

**EMBOLUS**

A blood clot within the circulation.

**EMBRYOLOGY**

The study of the early developmental stages of animals.

**EMESIS**

Vomiting.

**EMETINE**

$C_{29}H_{40}O_4N_2$ ; an alkaloid of ipecacuanha, used for amoebic dysentery.

**EMMENINS**

Naturally occurring esters of estrogenic hormones with glycuronic acid.

**EMODIN**

Frangulic acid; 4,5,7-trihydroxy-2-methyl-anthraquinone, obtained from rhubarb root, Cascara sagrada; m.p. 256-7°; a laxative.

**EMOTION, EFFECTS OF**

See Psychiatry Biochemistry of.

**EMPHESEMA, TISSUE**

See Toxicology.

**EMULSIN**

An enzyme found in bitter almonds and other places that hydrolyzes beta-glycosides into a sugar and a prosthetic group specific for the individual glycoside. Also called  $\beta$ -glycosidase.

**EMULSION**

A suspension of oil-in-water or water-in-oil. An emulsion may have dispersed particles larger than true colloids, which are stabilized by the presence of a (lyophilic) colloid, as in milk or egg yolk.

See also Enzymes, Non-Proteolytic.

**EMULSOID**

According to Wo. Ostwald, a colloidal suspension of a liquid in another liquid. Certain solids, such as gelatin, show all the properties of this class, so the term is not strictly accurate. Cf. Lyophilic.

**ENAMEL**

The epithelium-derived outer structure of teeth, the hardest tissue of the body; has 5% water,  $\alpha$ -keratin and inorganic matter, mostly hydroxy-apatite, and dahlite.

See Teeth, Biochemistry of.

**ENAMEL, MOTTLED**

See Fluorosis.

**ENCEPHALITIS**

An infectious, contagious disease due to a filtrable virus, attacking the central nervous system in acute and chronic forms. Lethargy is the most frequent symptom, with eye symptoms, as dip-



lopiā, strabismus, blurred vision, irregular pupils next. Muscular twitching and paralysis (Parkinsonian syndrome) may remain after recovery. Tremors, tics, spasms, speak of extensive damage to the vegetative nervous system. Autoserā are used with some success.

### ENDOCARDITIS

Inflammation of the endocardium. Classified clinically as simple, acute bacterial, subacute bacterial, atypical verrucous and terminal. Simple endocarditis or rheumatic endocarditis may be a complication of rheumatic fever or scarlet fever and is accompanied by damage to the heart valves. The bacterial forms are also referred to as "ulcerative" and are due to streptococcus, staphylococcus, pneumococcus, influenza bacillus, etc. They are very deadly. The atypical verrucous form (Libman-Sacks' Disease) combines many other rheumatic symptoms. A terminal form occurs following cancer, nephritis, etc. Treatments are symptomatic. So far chemotherapy or vaccine treatments or serotherapy have been failures.

### ENDOCRINES AND THE EMOTIONS

See Psychiatry, Biochemistry of.

### ENDOPEPTIDASE

See Proteinase.

### ENDOPLASM

The central portion of the cytoplasm of a cell.

### ENDOSMOSIS, ELECTRICAL

See Electrophoresis.

### ENDOTHERMIC

The absorption of heat by a system or an isolated reaction.

### ENDOTOXINS

See Microbiology.

### ENERGY, BIOTIC

See Biochemistry (Definitions).

### ENERGY, FREE

That portion of the total energy content of a system which is available for doing work. All forms of potential energy (mechanical, electrical, and chemical) constitute free energy in the presence of appropriate structural arrangements. Heat is convertible into work only in a fraction dependent on the difference of temperatures between which it is transferred, being completely convertible only with an infinite temperature drop.

### ENTEROGASTRONE

A hormone, postulated to be secreted by the gastric mucosa when there is fat in the intestine, and which inhibits gastric secretion and motility.

### ENTEROKINASE

Kinase specific for trypsinogen.

### ENTODERM

The embryonic gut or internal cellular layer of the embryo, formed from the materials situated around the vegetative pole of the egg.

### ENZYME INHIBITORS

See Enzymes, Non-Proteolytic.

### ENZYME SPECIFICITY

The specific relation of enzyme to substrate and reaction, manifested by the fact that a given enzyme will attack only a certain compound or group of compounds, and that different enzymes produce characteristically different reactions on the same substrate.

### ENZYMES

Definite material catalyzers of

organic and usually colloid nature with specific powers of reaction, formed by living cells, but usually independent of the presence of the latter in their operation. There are a great variety of them, and they are essential to most of the functions of the living organism.

#### ENZYMES, AUTOLYTIC

See Autolysis.

#### ENZYMES, COPPER PROTEIN

Copper containing enzymes which include the hemocyanins, polyphenol oxidase, monophenol oxidase (tyrosinase), laccase, hemocuprein, hepatocuprein, plant enzymes oxidizing ascorbic acid.

#### ENZYMES, CRYSTALLINE

The following enzymes or their precursors have been definitely crystallized: urease, catalase, pepsin, pepsinogen, trypsin, trypsinogen, chymotrypsin, chymotrypsinogen, carboxypeptidase, amylase, yellow respiratory ferment, ficin, papain, carbonic anhydrase, ribonuclease.

#### ENZYMES, HYDROLYTIC

May be classified as (1) esterases, which hydrolyze ester linkages, e.g. lipases, lecithinases, nucleases, phosphatases, sulfatases, choline esterase, cholesterase; (2) carbohydrases which hydrolyze glycoside linkages falling into groups of glycosidases, like sucrase, glycuronidases, etc., and polyases, like amylase, cellulase, cytases; (3) proteases which hydrolyze peptide linkages which fall into groups like peptidases, proteinases and amidases (hydrolytic deaminases).

#### ENZYMES, IRON PORPHYRIN PROTEIN

Oxidation catalysts containing a porphyrin structure, combined with iron, as hemoglobin, chloro-

crucorin, heliocorubin, catalase, peroxidase, cytochrome.

#### ENZYMES, NON-PROTEOLYTIC (HYDROLYTIC)

The biological catalysts of protein nature, known as enzymes, that are evolved by living cells for metabolic utilization, may be divided into two major groups: those effecting oxidations and reductions, and those producing hydrolysis. The latter group is made up of three main subdivisions representing the enzymes capable of hydrolysis, and in some cases the synthesis as well, of the three chief types of organic substances that compose living matter, i.e. proteins, carbohydrates, and lipids, and certain of their degradation products.

The present discussion is concerned with the hydrolytic enzymes that affect carbohydrates, lipids, and substances chemically related. These enzymes are classified in the table below, and it may be observed that in most cases the nomenclature follows the Duclaux system<sup>1</sup> by which enzymes are named by adding the suffix "ase" to the substrate on which the action occurs.

While enzymes may be differentiated for the most part by their specificity for particular substrates or structures, other factors offer not only additional differentiation between these enzyme types, but distinction between different enzymes acting on the same substrate. Thus the effect of pH, temperature, activators and inhibitors, the reaction kinetics, and physical separation often permit differentiation.

#### CARBOHYDRASES

##### Polysaccharidases

Amylases have been the most thoroughly studied members of this

group because starch and glycogen breakdown have been of great importance commercially and of particular interest in biology and medicine.

When starch or glycogen are subjected to enzymatic action the viscosity of the substrate is reduced with an accompanying liberation of phosphate and an increase in reducing power. This action is believed by some to result from an amylophosphatase<sup>2</sup> although no proof is now available that this enzyme is distinct from alpha-amylase that attacks the macromolecule to liberate dextrin units and some maltose. Beta-amylase breaks down the dextrin units to maltose and dextrans of lower molecular weight. There is evidence that the latter enzyme can also act directly on the starch molecule to whittle down the polysaccharide chain one maltose group at a time.<sup>2</sup> The iodine-coloring property of starch is destroyed by alpha-amylase, but it is not entirely removed by beta-amylase. Kuhn<sup>3</sup> was the first to classify amylases as alpha or beta on the basis of the mutarotation of the maltose formed, the alpha-amylase giving rise to alpha-maltose and the beta-enzyme to beta-maltose.

The amylases occur in the animal body mainly in saliva, pancreatic juice, and other digestive secretions, and also in organs actively involved in carbohydrate metabolism such as the liver. Clinical tests for the function of organs secreting large amounts of an enzyme have been evolved, based on the measurement of the concentration of the particular enzyme in the blood. Thus determination of amylase in blood serum has been employed as a test for pancreatic function. However abnormalities in other organs pro-

ducing the same enzyme must be considered in any interpretation of data of this nature as well as the physiological state of these organs at the time the blood is drawn. As a result the usefulness of these tests in general, and of the amylase test in particular, has been seriously limited.

In the plant organism amylases also occur particularly in those parts responsible for the metabolism of starch. This teleological trend is illustrated by the increase of amylase during the sprouting of seeds. Amylases are also found in a wide variety of fungi, bacteria, algae, and certain yeasts.

The fall in viscosity of starch solutions, the decrease in turbidity of glycogen solutions, the change in color given by iodine, and the more exact measurements of the increase in reducing substances, have all been employed to determine amylase activity. Details of these measurements, as well as procedures for the purification of amylases may be found in the standard reference works on enzyme methods.<sup>4-6</sup> The elegant micro- and ultra-micro technics of Linderstrøm-Lang and Holter have been applied to carbohydrases as well as the esterases to be discussed later.<sup>7, 8</sup>

Pancreatic and salivary amylases have been the most thoroughly studied in the animal body, and malt amylases, because of their position of prime importance to the brewing industry, have been the most completely investigated in the plant world. The pH optimum for the action of the former is 6.8 while that for the latter falls between 4.4 and 5.2. In considerations of pH-optima in general it should be borne in mind that these values are often influenced by factors such

as the nature of the buffers used, the presence or absence of salts and other compounds affecting activity, etc. Pancreatic amylase has been reported to have been produced in crystalline protein form.<sup>9</sup> The amylase of the fungus, *Aspergillus oryzae*, has attained importance in oriental food and beverage industries and in medicine.

Cellulase and lichenase, which may be the same enzyme, and cytase are polysaccharidases that attack plant framework substances. These have been found in the lower forms of life such as thermophilic bacteria, molds, fungi, snails, and ship worms that utilize cellulose and hemi-cellulose as sources of nutriment. They also occur in the endosperm of germinating barley, lupines, and palm seeds. There isn't a great deal known about these enzymes but it is striking that in the thermophilic bacteria, they may exhibit activity up to 70°.<sup>10</sup>

Inulinase, which breaks down inulin, the reserve carbohydrate of certain tubers and roots, to d-fructose has been found in all monocotyledonous plants, and in bacteria, yeasts and fungi. It has been claimed to occur in invertebrates, and in the spleen and placenta of some vertebrates. The optimum temperature for its action has been given as 55° and the optimum pH as 3.8.<sup>11</sup>

Most of the remaining polysaccharidases, also occurring in bacteria, fungi, and germinating seeds, and having optimum activity in acid media, require more thorough investigation before their properties, nature and possible uses can be established.

Hyaluronidase deserves especial mention since this enzyme is related

to the "spreading factor," an agent increasing tissue permeability and therefore concerned with the invasive ability of infective materials. Hyaluronic acid occurs in protective tissues such as skin and in bacterial capsules, and the enzyme attacking this polysaccharide lowers the viscosity of solutions of the substrate and liberates acetylhexosamine. Hyaluronidase is found in bacteria, testes, leeches, bee sting extracts, and some snake venoms. The activity of the enzyme is affected by salts, and two pH maxima for testicular preparations have been given, 4.4 and 5.8, while the single maximum, 5.8, has been reported for the enzyme from bacterial sources. At present, the question of the identity of the enzyme and the spreading factor cannot be considered completely settled. A practical application that may develop is suggested by the ability of hyaluronidase to destroy polysaccharide capsules of certain pathological streptococci. At the time of writing, no very complete review of the work on the enzyme has appeared; however a brief survey may be mentioned.<sup>12</sup>

In passing, attention should be called to the work of Dubos and Avery on the interesting enzyme obtained from a soil bacillus that digests the capsular polysaccharide of Type III pneumococci.<sup>13</sup> The injected enzyme can protect the mouse, rabbit, and monkey from the virulent organism.

#### Tetra and Trisaccharidases

Stachyase hydrolyses the tetrasaccharide, stachyose, to fructose and a mannosaccharide consisting of glucose and two molecules of galactose. This enzyme occurs in the digestive juices of crustaceans and mollusks as do the trisaccharidases, raffinase, capable of convert-

ing raffinose into fructose and melibiose, and gentianase, converting gentianose to fructose and gentiobiose. The trisaccharidases also occur in yeasts and *Aspergillus niger*. Raffinase, more extensively studied than the other enzymes, has been shown to have optimum activity at pH 4.5 to 5.0 at 30°. <sup>14</sup> *Aspergillus niger* also contains melezitase that hydrolyzes melezitose to glucose and turanose. The enzyme activity in all of these cases may be measured polariscopically or by the increase in reducing action.

#### Disaccharidases

Maltase splits maltose to two molecules of glucose. Although the enzyme occurs in digestive juices and organs where amylase is found, as well as in resting and germinating seeds, bacteria and fungi, most of the work has been carried out on yeast maltase. This enzyme is rather unstable and loses activity even at moderate temperatures; it is injured by low concentrations of alcohol, and is inactivated when its preparations are subjected to drying. The optimal conditions for activity are pH 6.7 to 7.3 and 40°. Willstätter and coworkers, who have carried out much of the work on maltase, have shown that the course of the hydrolytic reaction is greatly influenced by the nature of the enzyme preparation. <sup>15</sup>

Trehelase, a much more stable enzyme than maltase, hydrolyzes trehalose to two molecules of glucose. Little work has been done on this enzyme but it is as widely distributed in plant and animal life as maltase itself and appears to have greatest activity in slightly acid media.

Saccharase is one of the most

thoroughly studied enzymes known. Its conversion of saccharose to glucose and fructose is a process of industrial importance, and the accuracy of the polarimetric method by which the course of the hydrolysis may be followed, has enabled this reaction to be studied as a model in more purely scientific investigations. The work of Nelson <sup>16</sup> on the kinetics of the enzyme action is classical. The saccharase studies of Michaelis and Menten <sup>17</sup> led to the theory that enzyme and substrate combined to form an enzyme-substrate compound that breaks down to yield the free enzyme and the reaction products. The velocity of the hydrolysis is determined by the concentration of the intermediate enzyme-substrate compound, and the affinity between enzyme and substrate can be expressed quantitatively in terms of the dissociation constant of this compound. The Michaelis theory was used later to explain the mode of action of enzyme inhibitors, <sup>18</sup> so called "competitive" inhibition results from the inhibiting substance combining with the enzyme, in competition with the substrate, to form an enzyme-inhibitor compound thus reducing the concentration of the enzyme-substrate compound. This type of inhibition varies with the substrate concentration. "Non-competitive" inhibition results from the inhibiting substance reducing the decomposition velocity of the enzyme-substrate compound, but the inhibitor displays no affinity for the enzyme and the inhibition is independent of the substrate concentration.

Saccharase occurs in the intestines of higher animals and in the honey vesicles, saliva, and intestines of bees and other insects utilizing

saccharose; but it is much more widely distributed in the plant kingdom, being particularly prevalent in those parts acting as carbohydrate stores, such as the sugar beet root. The abundance of the enzyme in yeasts has made these its chief source. The pH optimum for the yeast enzyme is 4.5, while for intestinal saccharase it falls between 5.0 and 7.0. The enzyme is inactivated by oxidizing agents, heavy metal salts, alcohol, and acetone; it is inhibited by the products of its action and is relatively insensitive to neutral salts.

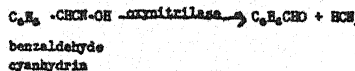
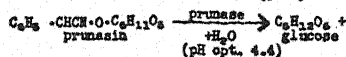
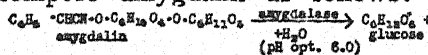
Cellobiase and gentiobiase convert their respective substrates to glucose. Both occur in many seeds, grains, fungi, and bottom yeasts, and they are found together, usually in the presence of lichenase as well. The optimum pH has been given as 6.0 and the optimum temperature as 46°.

Lactase and melibiase, the galactosidases producing glucose and galactose as their hydrolytic products, are both found in bitter almonds. However only the latter occurs in bottom-yeasts while the former is prevalent in milk sugar yeasts, a number of fungi, fetal intestines, and certain bacteria. Little is known about melibiase, but it has been determined that its pH optimum is 5.5; that for almond lactase is 4.2 to 4.6, for the yeast enzyme 7.0, and for various intestinal lactases 5.0 to 6.4. The lactase of *Escherichia coli* has received especial consideration because it offers a classical example of the adaptive production of enzymes by bacteria.<sup>19</sup> This bacterial species does not produce lactase unless the organisms are transferred repeatedly in lactose broth, whereupon the enzyme is generated rapidly. Another ex-

ample of enzyme adaptation is offered by bacteria that form the enzymes that hydrolyze capsular polysaccharides of pneumococci; the enzymes adaptively developed for the hydrolysis of Type III polysaccharide have no action against the Type VIII substance.

### Other Glucosidases

Emulsin is the name given to the mixture of enzymes that decompose amygdalin as follows:—



The enzyme obtained from bitter and sweet almonds produces all of the above changes and it has been the contention of Weidenhagen<sup>20</sup> that a single enzyme is responsible for the hydrolysis of all beta-d-glucosides and oligosaccharides with a beta-d-glucosidic linkage including cellobiose and gentiobiose. Helferich and coworkers, who have made many studies on emulsin, found that anions of neutral salts strongly activate the enzyme from sweet almonds.<sup>21</sup> The early work of Bourquelot elucidated the hydrolytic and synthetic characteristics of these enzymes, and recent studies by Pigman<sup>22</sup> on the relation between substrate structure and emulsin action are noteworthy.

Myrosinase hydrolyzes myrosin or sinigrin to glucose, mustard oil (allylthiocyanate), and  $\text{KHSO}_4$ . The enzyme occurs in black mustard seed and other Cruciferae; it has a pH optimum around 7.0 and a temperature optimum of 45 to 50°.

Nucleosidase converts nucleosides



to ribose and adenine. The enzyme, one of a series involved in the breakdown of nucleic acids that have been studied particularly by Levene and coworkers,<sup>23</sup> is found in kidney, spleen and pancreas of cattle, and in intestinal juices of dogs. It has optimum activity at pH 7.5 and 37°.

## ESTERASES

### Lipases

Lipases hydrolyze neutral fats, glycerides of higher fatty acids, to glycerol and fatty acid. In the animal body the pancreas is the richest source of this enzyme although it occurs in rather high concentration in all of the digestive organs. It was thought earlier that stomach lipase had optimum activity between pH 4.0 and 5.0 in contrast to the enzyme in other organs that exhibit maxima from 7.0 to 8.6 depending on the source. However, Willstätter and coworkers<sup>24</sup> have shown this to be due to the effects of concomitant materials naturally present, and the difference disappears on enzymatic purification. The activation of lipase action by bile salts is of physiological interest, but a variety of other surface active substances in low concentration can also produce activation. The activation effected by calcium and other salts must be considered in measurements of lipase activity.

Determinations of activity for most of the esterases are based on measurement of the acid liberated. Titration, manometric, colorimetric, and stalagmometric methods have all been employed. The methodology and preparative details are available in standard reference works.<sup>4-6</sup>

The Ricinus lipase of castor beans has been investigated more completely than the enzyme from

other plant sources. The active enzyme is insoluble in aqueous media. Although the lipase from ungerminated seeds has maximum activity at pH 4.7 to 5.0, the activity at higher pH values gradually increases during germination.<sup>25</sup> This change can also be produced by treating the seed enzyme with pepsin.

Lipases, as well as the simple organic esterases to be discussed next, can also synthesize esters from alcohol and acid. Sym<sup>26</sup> has developed procedures for these enzymatic syntheses employing practically non-aqueous media.

### Simple Organic Esterases

These esterases, liberating alcohols and simple organic acids from their esters, are found in particularly high concentration in liver. The specificity differences between these esterases and the lipases, first demonstrated by Loevenhart, have been extensively elaborated by Willstätter and his colleagues and others. Further differences between the esterases and lipases are found in their protein nature, kinetics, and influence of foreign substances.<sup>27</sup> The stereochemical specificity of these enzymes<sup>28</sup> is quite marked, and it appears to be a property of the enzyme itself and not the result of accompanying materials in the preparation. The inhibitors of liver esterase also exhibit stereochemical specificity. The enzyme is inhibited by high concentrations of its own substrates.

Hydrolysis by liver esterase follows a zero molecular reaction course due to the very high affinity for its substrate<sup>27</sup> and the pH optimum ranging from 6.7 to 8.8 has been found to be influenced by the nature of the buffer, substrate, and enzyme source.

### Cholesterol esterase

This enzyme hydrolyzes cholesterol esters to the free alcohol and organic acids, usually the latter are higher fatty acids; and it has been shown that these esters can be enzymatically synthesized by the method of Sym previously mentioned. Cholesterol esterase has been found in the liver, spleen, nerve tissue, and blood, and the chief interest in the enzyme is its relation to resorption and transport of fat in the animal body.

### Azolesterases

Azolesterases are defined as the enzymes that hydrolyze esters of nitrogen—alcohols, and they have been shown to be distinct from simple organic esterases in both distribution and properties.

Cholinesterase, first demonstrated by Loewi and coworkers, has received more attention than other members of this group because of its interesting relation to the transmission of nerve impulses. The enzyme can hydrolyze, not only the physiologically important acetylcholine, but a wide variety of chemically related esters in which the alcohol component may contain a nitrogen-heterocyclic ring instead of a substituted nitrogen group. Replacement of the nitrogen in the ester by arsenic or phosphorus does not change the enzyme action, and thiocholine esters are hydrolyzed even faster than the choline compounds. The presence of a nitrogen group in the acid component of the ester prevents any enzyme action.<sup>29</sup>

The richest sources of the enzyme are salivary and lachrymal glands, alimentary mucosa, and tissues of the nervous system. Optimum activity is obtained at pH 8.5 and 40°. The powerful inhibition of the en-

zyme by traces of physostigmine is utilized in physiological experimentation. Thiamin also inhibits the enzyme, and neutral salts and calcium ion have a definite activating effect.

Of the tropinesterases, atropinesterase was first investigated by pharmacologists interested in the destruction of atropine in the animal body. The enzyme produces tropine and tropic acid from the alkaloid. Some rabbits contain atropinesterase while others do not, evidence that this enzyme is identical with the "alkaline" phosphomonoesterase mentioned above.<sup>34</sup>

Phytase hydrolyzes phytin to inositol and phosphoric acid. The enzyme is distributed in liver and blood of animals, fungi, and especially in seeds and malt. The pH optimum for the malt enzyme is 5.6 and Sawin and Glick have shown this enzyme to be an incompletely dominant hereditary factor in the rabbit. Serum, liver, and intestinal mucosa are particularly rich in the enzyme, and its optimum activity is found in pH 8.1 to 8.4 and 38°. The hydrolysis follows a zero molecular reaction course, and the enzyme is activated by neutral salts and inhibited by sulfhydryl compounds, physostigmine, cyanide and fluoride.

Tropacocainesterase and cocainesterase hydrolyze tropacocaine and cocaine respectively to tropine and benzoic acid in the first case, and probably ecgonine, benzoic acid and methyl alcohol in the second. The uncertainty about the cocaine scission derives from the fact that the products have not been isolated and the possibility remains that the enzyme may hydrolyze only one of the two ester groups in the sub-

strate. The existence of the three tropinesterases as separate enzymes requires further evidence since the present differentiation is based only on differences in their occurrence in the blood of various species.<sup>30</sup> These enzymes, in addition to cholinesterase, are contained in the alpha and beta globulin fractions of blood sera.

Morphinesterase, discovered by Wright,<sup>31</sup> hydrolyzes the alcoholic acetyl group from mono- or diacetyl morphine. The enzyme is found in the sera of only some rabbits, and since it appears to parallel the occurrence of atropinesterase the possibility arises that the two enzymes may be identical.

#### Chlorophyllase

Chlorophyllase, discovered by Willstätter and Stoll<sup>32</sup> converts chlorophyll to phytol and chlorophyllide. As would be expected, it is present in all green plant life. The enzyme retains activity in strong alcohol solutions and in the presence of acetone, and when the enzymatic action occurs in alcohol media an alcohololysis occurs by which ethylchlorophyllide is formed. The synthetic properties of the enzyme also enable formation of chlorophyll, from the acid and phytol.

#### Tannase

The identity of tannase as a single enzyme is still an open question. The enzyme liberates phenolcarboxylic acids and alcohols from tannins and peptides. Methyl gallate is commonly used as the substrate in tannase investigations. Many properties of the enzyme have not yet been established. It is found chiefly in molds and fungi, and for its action it requires that the acid component of the substrate

contain at least two phenolic hydroxyl groups which may not be ortho to the carboxyl radical.

#### Sulfatase

Sulfatase, first described by Neuberger, effects the cleavage of phenolic sulfuric acid esters. These compounds are formed by the detoxication mechanisms in the animal body for the elimination of phenols. The enzyme is found in kidney and muscle, and also in molds and fungi. An extensive review of the subject has appeared recently.<sup>33</sup>

#### Phosphatases

Phosphomonoesterases<sup>34</sup> affect diverse substrates to liberate orthophosphoric acid and alcohol components such as glycerol. These enzymes are highly important in the fat, carbohydrate, and mineral intermediate metabolisms. The measurements of serum "acid" and "alkaline" phosphatases that hydrolyze beta-glycerophosphate are used in medicine for diagnosis and prognosis of prostate cancer and bone disease. The "acid" enzyme occurring particularly in the prostate, liver, pancreas, and rice bran operates best at a pH of about 5.0, and the "alkaline" enzyme found especially in kidney, leucocytes, intestine and bone tissue is most active around a pH of 9.0. The former enzyme is not activated by magnesium ion but the latter is. A glycerophosphatase having its pH optimum at 3.0 to 4.0 is found in molds and fungi, and this enzyme is activated by magnesium ion when the substrate is alpha-glycerophosphate, but inhibited by the same ion when beta-glycerophosphate is used. Mammalian erythrocytes contain a glycerophosphatase having a pH optimum at 6.0 that is activated by magnesium ion. In

contrast to the other glycerophosphatases, this enzyme hydrolyzes the alpha-substrate faster than the beta.

Nucleotidase breaks down nucleotides to a carbohydrate-purine or -pyrimidine base and phosphoric acid. It has been demonstrated in glandular tissues, nerves, and blood.<sup>23</sup> There is a good deal of evidence that this enzyme is identical with the "alkaline" phosphomonoesterase mentioned above.<sup>34</sup>

Phytase hydrolyzes phytin to inositol and phosphoric acid. The enzyme is distributed in liver and blood of animals, fungi, and especially in seeds and malt. The pH optimum for the malt enzyme is 5.6.

Hexosediphosphatase has not been proven to be a distinct enzyme although its preparations are devoid of activity on glycerophosphates.<sup>34</sup> The enzyme plays an important role in alcoholic fermentation through its effect on fructose diphosphate, and it is also involved in the carbohydrate conversion in muscle. The particular hexosemonophosphate formed by the kidney or yeast enzyme is conditioned by the presence of arsenate.

Phosphodiesterases<sup>34</sup> hydrolyze one ester linkage in diesterorthophosphates. These enzymes occur in yeasts, rice bran, snake venoms, and animal tissues. The pH optimum of the enzyme in rice bran is 5.5 and in snake venom 8.6. Since these enzymes produce monoesters, their action must be followed by phosphomonoesterase to effect the complete liberation of phosphoric acid. Lecithinases belong to this group since they hydrolyze the diglyceride esters of phosphocholine known as lecithins. These enzymes are found in many animal tissues

but particularly in the kidney. A pH optimum of 7.5 has been reported. Phosphotriesters are not hydrolyzed by any known enzyme.

## OTHER HYDROLYTIC ENZYMES

### Pyrophosphatases

The term, pyrophosphatases, is employed in the present instance to denote those enzymes capable of hydrolyzing the intramolecular linkages between the phosphorus units themselves in polyphosphorus compounds. This group of enzymes is of great importance in the intermediate carbohydrate metabolism of muscle.

Adenosinetriphosphatase converts adenosinetriphosphate to adenosinediphosphate. The brilliant work of Ljubimova and Engelhardt<sup>35</sup> has shown that myosin, the chief protein of muscle, is probably identical with this enzyme. Confirmations have been forthcoming from Needham, Bailey, and others at Cambridge.<sup>36</sup> Thus the new concept arises that an enzyme may exist, not only as a small amount of catalytic material in a bulk of tissue, but also as the main mass of a tissue. The enzyme is very unstable, losing activity at slightly elevated temperatures (40°) and when subjected to weak acidities (up to pH 4.0); it is inactivated by urea, and traces of silver ion abolish all activity. In this connection mention should be made of the crystallization of myogen,<sup>35</sup> the second most prevalent protein in muscle, by Baranowski. This protein appears to be identical with an aldolase effecting decomposition of glucose.

Thiaminpyrophosphatase is of physiological interest since its substrate, thiaminpyrophosphate or co-carboxylase, is important in body

oxidation mechanisms. The enzyme occurs in yeast and a pH optimum of 3.7 has been reported.<sup>37</sup>

### Phosphorylase

While a discussion of the many steps in carbohydrate metabolism is beyond the scope of the present article, attention should be drawn to one of the more important phosphatases, phosphorylase, involved in the reversible glucose-1-phosphate  $\rightleftharpoons$  glycogen or starch transformation. This enzyme has been investigated particularly by Cori and coworkers<sup>38</sup> who have shown that, in the case of the animal enzyme, adenylic acid is essential for activity. Reducing agents enhance the activity, and the presence of some glycogen is necessary for the progress of the synthetic reaction. Change in pH produces a shift in the equilibrium finally attained. A typical glycogen is formed by the enzyme from liver, heart, or brain tissue, but the polysaccharide produced by muscle phosphorylase, in common with the enzyme from plant sources, is more like starch.

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### BIBLIOGRAPHY

- <sup>1</sup> Duclaux, E., *Microbiologie*, 141 (1883).
- <sup>2</sup> Hanes, C. S., *New Phytologist*, 36: 101, 189 (1937).
- <sup>3</sup> Kuhn, R., *Ann.*, 444: 1 (1925).
- <sup>4</sup> Rona, P., *Praktikum der Physiologischen Chemie, I. Fermentmethoden*, 2nd. Ed., Berlin (1931).
- <sup>5</sup> Oppenheimer, C., *Die Fermente und ihre Wirkungen*, III, 5th Ed., Leipzig, 1924-26.
- <sup>6</sup> Bamann, E., and Myrbäck, K., *Die Methoden der Fermentforschung*, Leipzig, 1940-1.
- <sup>7</sup> Linderström-Lang, K. and Holter, H., *Ergebnisse der Enzymforschung*, 3: 309 (1934), and p. 1132-1162 in Myrbäck and Bamann ref. 6.
- <sup>8</sup> Glick, D., *J. Chem. Education*, 12: 253 (1935); 16: 68 (1939).
- <sup>9</sup> Caldwell, M. L., Booher, L. E. and Sherman, H. C., *Science*, 74: 37 (1931).
- <sup>10</sup> Pringsheim, H., *Z. physiol. Chem.*, 78: 266 (1912).
- <sup>11</sup> Pringsheim, H. and Kohn, G., *Z. physiol. Chem.*, 133: 80 (1924).
- <sup>12</sup> Glick, D., *Ann. Rev. Biochem.*, 11: 55 (1942).
- <sup>13</sup> Dubos, R. J., *Ergebnisse der Enzymforschung*, 8: 135 (1939).
- <sup>14</sup> Willstätter, R. and Kuhn, R., *Z. physiol. Chem.*, 115: 180 (1921).
- <sup>15</sup> Willstätter, R. and Steibelt, W., *Z. physiol. Chem.*, 115: 199 (1921).
- <sup>16</sup> Nelson, J. M., *Chem. Reviews*, 12: 1 (1933).
- <sup>17</sup> Michaelis, L. and Menten, M. L., *Biochem. Z.*, 49: 333 (1913).
- <sup>18</sup> Michaelis, L., et al., *Biochem. Z.*, 60: 62, 79 (1914).
- <sup>19</sup> Dubos, R. J., *Bact. Reviews*, 4: 1 (1940).
- <sup>20</sup> Weidenhagen, R., *Ergebnisse der Enzymforschung*, 1: 168 (1932).
- <sup>21</sup> Helferich, B. and Schmitz-Hillebrecht, E., *Z. physiol. Chem.*, 234: 54 (1935).
- <sup>22</sup> Pigman, W. W., *J. Res. Natl. Bur. Stads.*, 26: 197; 27: 1 (1941).
- <sup>23</sup> Levene, P. A. and Bass, L. W., *Nucleic Acids*, New York, 1931.
- <sup>24</sup> Willstätter, R., et al., *Z. physiol. Chem.*, 133: 247 (1923); 140: 203 (1924), 144: 68 (1925).
- <sup>25</sup> Willstätter, R. and Waldschmidt-Leitz, E., *Z. physiol. Chem.*, 134: 161 (1923).
- <sup>26</sup> Sym, E. A., *Enzymologia*, 1: 156 (1936).
- <sup>27</sup> Sobotka, H. and Glick, D., *J. Biol. Chem.*, 105: 199 (1934).
- <sup>28</sup> Rona, P. and Ammon, R., *Ergebnisse der Enzymforschung*, 2: 50 (1933).
- <sup>29</sup> Glick, D., *Biological Symposia*, 5: 213 (1941).
- <sup>30</sup> Glick, D. and Glaubach, S., *J. Gen. Physiol.*, 25: 197 (1942).
- <sup>31</sup> Wright, C. I., *J. Pharmacol.*, 71: 164 (1941); 75: 328 (1942).
- <sup>32</sup> Willstätter, R. and Stoll, A., *Ann.*, 378: 18 (1910); 380: 148 (1911).
- <sup>33</sup> Fromageot, C., *Ergebnisse der Enzymforschung*, 7: 50 (1938).

# DICTIONARY OF BIO-CHEMISTRY

<sup>34</sup> Folley, S. J. and Kay, H. D., *Ergebnisse der Enzymforschung*, 5: 159 (1936).

<sup>35</sup> Engelhardt, W. A., *Adv. in Contemporary Biol.*, XIV, Moscow (1941).

<sup>36</sup> Needham, J., Kleinzeller, A., Miall, M., Dainty, M., Needham, D. M. and

Lawrence, A. S. C., *Nature*, 150: 46 (1942).

<sup>37</sup> Westenbrink, H. G. K., van Dorp, D. A., Gruber, M. and Veldman, H., *Enzymologia*, 9: 73 (1940).

<sup>38</sup> Cori, C. F., *Biological Symposia*, 5: 131 (1941).

## CLASSIFICATION

<u>NAME</u>	<u>SYNONYMS</u>	<u>SUBSTRATE</u>	<u>PRODUCTS</u>
<b>I. Carbohydrases</b>			
<b>A. Polysaccharidases</b>	Polyases		
1. Amylase:	Diastase, Amylopsin	Starch, glycogen	Dextrins + Maltose
a. amylolphosphatase		" "	Phosphate + Simpler polysaccharides.
b. alpha-amylase		" "	Chiefly dextrins
c. beta-amylase		" ", dextrins	Maltose + Dextrins
2. Cellulase		Celluloses	Cellulobiose
3. Lichenase		Lichenin	Cellulobiose
4. Cytase		Hemicelluloses, mannans, galactans, pentosans	Dextrins + Monosaccharides
5. Inulase		Inulin	Fructose
6. Pectinase	Pectase	Pectic materials	Pentoses + Galactose
7. Seminase		Mannogalactans	Mannose + Galactose
8. Chitinase		Chitin	
9. Hyaluronidase		Hyaluronic Acid	Aldobionic Acid Unit + Acetylhexosamine
10. Polysaccharidase of Dubos and Avery		Capsular Polysaccharide of Pneumococci	
<b>B. Tetra- and Trisaccharidases</b>			
1. Stachyase		Stachyose	Fructose + Mannosaccharide
2. Raffinase		Raffinose	Fructose + Melibiose
3. Gentianase		Gentianose	Fructose + Gentiobiose
4. Melezitase		Melezitose	Glucose + Turanose
<b>C. Disaccharidases</b>			
1. Alpha-hexosidases			
a. alpha-glucosidases			
i. maltase		Maltose	Glucose + Glucose
ii. trehalase etc.		Trehalose	Glucose + Glucose
b. alpha-fructosidases			
i. saccharase etc.	Invertase, sucrase	Saccharose	Fructose + Glucose
2. Beta-hexosidases			
a. beta-glucosidases			
i. cellobiase	Cellase	Cellulobiose	Glucose + Glucose
ii. gentiobiase etc.		Gentiobiose	Glucose + Glucose
b. beta-galactosidases			
i. lactase		Lactose	Glucose + Galactose
ii. melibiase etc.		Melibiose	Glucose + Galactose

(Classification II and III on next page)

## ENZYMES, PROTECTIVE

Enzymes formed in the body as a result of the presence in the blood of foreign substances, which the enzymes split up and thus protect the organism.

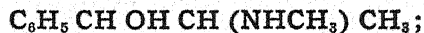
## ENZYMES, PROTEOLASTIC

Enzymes which split up the protein molecule.

## ENZYMES, PYRIDINOPROTEIN

Enzymes whose prosthetic groups contain pyridine derivatives.

## EPHEDRINE



An alkaloid from the Chinese drug Ma Huang; also prepared synthetically. It is dextrarotatory, but has laevorotatory salts. It raises blood pressure, strengthens heart action, and can be taken orally.

## EPHEDRINE TESTS

See Ekkert, Kelly.

## EPIDEMIOLOGY

See Microbiology.



# DICTIONARY OF BIO-CHEMISTRY

## Enzyme Classification (Continued)

NAME	SYNONYMS	SUBSTRATE	PRODUCTS
<b>I. Other Glucosidases</b>			
a. emulsin (amygdalinase, prunase, oxynitrilase)		Amygdalin	Glucose + Glucose + Benzaldehyde + HCN
b. myrosinase	Sinigrinase	Myrosin	Glucose + Allylisothiocyanate + $\text{KHSO}_4$
c. nucleosidase		Nucleosides	Ribose + adenine
<b>II. Esterases</b>			
A. Lipases	Steapsin	Fats and Oils	Glycerol + Higher Fatty Acids
B. Simple Organic Esterases		Simple Organic Esters	Alcohols + Lower Fatty Acids
C. Cholesterolsterase	Cholesterinase	Cholesterol Esters	Cholesterol + Fatty Acids
D. Azolesterases			
1. Cholinesterase		Choline- and related esters	Choline or related nitrogen alcohols + organic acids
2. Tropinesterases			
a. atropinesterase		Atropine	Tropine + Tropic Acid
b. tropacocainesterase		Tropacocaine	Tropine + Benzoic Acid
c. cocainesterase		Cocaine	Probably, Ecgonine + Benzoic Acid + Methyl Alcohol
3. Morphinesterase		Monoacetylmorphine	Morphine + Acetic Acid
E. Chlorophyllase		Chlorophyll	Phytol + Chlorophyllide
F. Tannase		Tannins and Phenol-carboxylic acid esters	Alcohol + Phenolcarboxylic acids
G. Sulfatase		Ethereal Sulfates	Phenols + Sulfuric Acid
H. Phosphatases			
1. Phosphomonoesterases			
a. "alkaline" and "acid" phosphatases		Glycerophosphates	Glycerol + $\text{H}_2\text{PO}_4$
b. nucleotidase		Phenylphosphates, etc.	Phenol + $\text{H}_2\text{PO}_4$
c. phytase		Nucleotide	Nucleoside + $\text{H}_2\text{PO}_4$
d. hexosediphosphatase		Phytin	Inositol + $\text{H}_2\text{PO}_4$
2. Phosphodiesterases		Hexosediphosphate	Hexosemonophosphate + $\text{H}_2\text{PO}_4$
		1-glycerolphosphate	Glycerol + Monoglycerolphosphate
		Diphenylphosphate	Phenol + Monophenylphosphate
	Lecithinases	Lecithin	Diglyceride + Phosphocholine, or Choline + Diglyceride Phosphate
<b>III. Other Hydrolytic Enzymes</b>			
A. Pyrophosphatases			
1. Adenosinetriphosphatase		Adenosinetriphosphate	Adenosinediphosphate + $\text{H}_2\text{PO}_4$
2. Adenosinediphosphatase		Adenosinediphosphate	Adenosinemonophosphate + $\text{H}_2\text{PO}_4$
3. Thiaminpyrophosphatase		Thiaminpyrophosphate	Thiaminphosphate + $\text{H}_2\text{PO}_4$
4. Other Pyrophosphatases		Diphenylpyrophosphate, etc.	Diphenylphosphate + $\text{H}_2\text{PO}_4$
B. Phosphorylase		Glucose-1-phosphate (Cori-ester)	Starch or Glycogen + $\text{H}_2\text{PO}_4$

## EPILEPSY

Falling sickness; a complex of symptoms of seizures of sudden loss of consciousness often accompanied by convulsions, attributed to injury to the central nervous system which may be congenital or acquired as in brain tumors, fractures of the skull and

many diseases (cerebral arteriosclerosis, endocrine dysfunction, syphilis, heart block, etc.). Adrenalin and pituitrin predispose to attack on direct administration. Constipation, menstruation and allergy are precipitating factors. Fundamentally alkalosis and oxygen lack lead to edema and in-

creased intracranial pressure affects the nerve cells so as to produce muscular spasm. The major types of attack are: (1) grand mal, convulsions followed by coma and (2) petit mal, a sudden helplessness and brief unconsciousness. Jacksonian epilepsy is a progressive form, beginning with the muscles on one side. Nocturnal epilepsy may occur for long times in the sleep. Pyknolepsy is a form of frequent momentary unconsciousness occurring in young children without complications till it leaves at puberty.

Epileptic equivalents are forms of unconsciousness without convulsions. Narcolepsy is a form in which drowsiness occurs with sudden sleep. Catalepsy is a sudden weakness in the legs under emotional stress.

The treatments are causal. Ketogenic diets are frequently recommended, and so are salt-poor diets. Sedatives must be used carefully, sometimes removal of bone pressure on the brain is adequate if that is causal.

See also Psychiatry, Biochemistry of.

#### EPINEPHRINE

1-(beta-methylamino, alpha-3, 4-dihydroxyphenyl)-ethanol; the active ingredient of the adrenaline glands; causes marked contraction of the blood vessels, with a corresponding rise in blood pressure.

#### EPINEPHRINE TESTS

See Azzolini, Bayer, Ekkert, Folin, Kisch, Paget, Pellerin, Russmann, Velicogna.

#### EPININE

A commercial preparation of 1-epinephrine hydrochloride.

#### EPIPHYSIS

(1) Pineal gland; (2) separately ossified cartilagenous material joined to a main bone.

#### EPPINGER TEST FOR GLYOXYLIC ACID

A mixture of glyoxylic acid and 0.1% indole solution is floated on concentrated sulfuric acid; a red ring is formed. Skatole may be used for indole. Sensitivity — 1:20000.

Reference: Zeit. anal. Chem. 1907, 270.

#### EQUILENIN

$C_{18}H_{18}O_2$ ; m.p. 258-259°; an estrogenic hormone found in pregnant mare urine. Its structure is that of estrone with two double bonds in ring II, and it has 1/16 of its potency.

#### EQUILENIN TEST

See Marx-Sobotka.

#### EQUILIN

$C_{18}H_{20}O_2$ ; m.p. 283-240°; an estrogenic hormone found in pregnant mare's urine. It has one alicyclic double bond more than estrone, and has 1/7th of its potency.

#### EREPSIN

See Peptidase.

See also Autolysis.

#### ERG

A unit of work used in the metric system defined as the amount of work done in raising one gram one centimeter.

#### ERGAMINE

Old name for histamine.

See Ergot.

#### ERGOBASINE

Ergometrine.

See Ergot.

#### ERGOCLAVINE

See Ergot.

**ERGOCRISTINE**

See Ergot.

**ERGOCRISTININE**

See Ergot.

**ERGOMETRINE**

See Ergot.

**ERGOMETRININE**

See Ergot.

**ERGOMONAMINE**

See Ergot.

**ERGONOVINE**

Ergometrine.

See Ergot.

**ERGOSINE**

See Ergot.

**ERGOSININE**

See Ergot.

**ERGOSTEROL**

$C_{28}H_{44}O$ ; m.p.  $163^{\circ}$ ; a sterol of ergot and yeast, having an OH at  $C_3$ , a 9 carbon chain with one double bond at  $C_{17}$  and a double bond at  $C_{5-6}$  and at  $C_{7-8}$ . On irradiation by ultraviolet light, yields successively at least five isomers; tachysterol, lumisterol, the anti-rachitic calciferol, or vitamin  $D_2$ , and suprasterol I and II.

H. S.

See Radiation, Biological Effects of.

**ERGOSTEROL TESTS**

See Brückner, Levine-McKay, Montignie, Rosenheim, Tortelli-Gaffe.

**ERGOSTETRINE**

Ergometrine.

See Ergot.

**ERGOT**

Ergot is a fungus which grows in the heads of cereal grains and grasses. The ergot of medicinal importance, and the only one recognized in the United States Pharmacopoeia XII, is that which develops

on rye due to the particular fungus *Claviceps purpurea*. The young rye flowers are infected by the ascospores of the fungus, which then develop in and replace the grain of the rye. The sclerotium thus formed is a slender, cylindrical, somewhat curved and longitudinally furrowed body, larger than the grain which it has replaced. Several such kernels or sclerotia may be found in a single head of rye. The name ergot comes from the French word for cock's spur, from the fancied resemblance of the sclerotia to this structure. Ergot shipped to the United States has come largely from Spain and Russia.

The presence of ergot in rye, as well as in other cereal and forage grains and grasses has frequently led in the past to widespread and serious epidemics of poisoning. The Saint Anthony's fire of the middle ages is now believed to have been ergotism. No serious poisoning from ergot contaminated flour has occurred in the United States for many years, although injury to stock from eating heavily infested grasses has been reported a number of times.

The powerful activity of ergot has led to extensive studies of both its chemistry and its pharmacology over many years. No other fungus, and few if any plants or plant products have been the subject of so much investigation. From ergot there have been isolated a large number of substances of biochemical interest, some of which are specific to ergot, while others are of more general distribution. The pharmacological properties of histamine were discovered largely because of an interest in ergot extracts, and the name ergamine is still sometimes applied to histamine.

Ergosterol and ergothioneine (thioneine) were named from ergot where they were first found to occur.

Of the substances peculiar to ergot the alkaloids are most important. Present day views ascribe all or nearly all of the pharmacological activity of ergot to these substances. While extracts of ergot may contain other highly active substances such as histamine, tyramine, acetylcholine, these are either destroyed or rendered ineffective in the gastrointestinal tract, so that they probably played no role either in the therapeutic action of galenical ergot preparations, such as the extract, or in the poisoning from eating ergotized rye.

Isolation of the alkaloids has been difficult. Not all of those known are present in every sample of ergot. Their relative proportions vary. Even different sclerotia from one head of rye may have different amounts of alkaloids. Crystallization of some has proved difficult. Frequently crystallization with molecules of solvent occurs, and removal of these has not been easy. Many of the chemical and pharmacological studies have been carried out with incompletely purified materials. The terminology has been correspondingly confused. Current views recognize the existence of five pairs of optically active alkaloids, interconvertible isomerides, either existing as such in ergot or readily obtained by isomerization from the naturally occurring alkaloids. These pairs are: ergotinine and ergotoxine; ergotamine and ergotaminine; ergometrine (see below) and ergometrinine; ergosine and ergosinine; ergocristine and ergocristinine. (The alkaloid ergometrine was discovered more or less

simultaneously by four different groups of workers in different parts of the world, and called also ergobasine, ergotocin, ergostetrine. The Council on Pharmacy and Chemistry of the American Medical Association adopted the name ergonovine, which term is now official in the United States Pharmacopoeia XII. (The form ergometrine is used in the present paragraph to emphasize the relationship to the inactive isomer ergometrinine.) Other alkaloids have also been described. Sensibamine is a complex (apparently equimolecular) of ergotamine and ergotaminine. Ergoclavine is a similar complex of ergosine and ergosinine. Further complications are added through the description of similar complexes between the active isomer of one pair, and the inactive member of another pair; e.g., ergosine and ergotaminine, ergosinine. Some fourteen such complexes have been reported, with details of crystallographic structure. While such complexes might be expected to show pharmacological activity representing the average of the two components, according to Barger such evidence as is available "imperfectly supports this view." A recently described alkaloid of smaller molecular weight, ergomonomine,  $C_{19}H_{19}NO_4$ , evidently belongs to a different series. It is not an indole derivative.

These substances are all alkaloids in the generally accepted sense of the term. They are soluble in organic solvents (excepting petroleum ether), and sparingly soluble or insoluble in water with the exception of ergometrine and ergometrinine. In most cases they form salts which can be crystallized. Their structure is imperfectly known. On hydrolysis the largest

Table 1

Substances	Specific Rotation in chloroform	Crystalline Form	Melting Point
3-Ergotamine $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +333$ (A) $[\alpha]_D^{20} = +325$ c = 1%	Long needles, sides not parallel; and symmetri- cally replaced by a pair of faces, and the extinction is straight	245°
Ergotamine $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +326$ (A) $[\alpha]_D^{20} = +197$ c = 1%	Six-sided prisms from benzene	190°-200°
Ergotamine $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +181$ (A) $[\alpha]_D^{20} = +158$ c = 0.6%	Irregular plates (a quaternary acetate) Long prisms (benzene)	214° (Cor.)
Ergotamine $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +450$ (A) $[\alpha]_D^{20} = +388$ c = 0.6%	Plates (alcohol)	228° (Cor.)
Ergotamine (Ergotamine) $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +44$ (A) $[\alpha]_D^{20} = +90$ (in water) c = 0.05%	Needles	150°-160°
Ergotamine $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +320$ c = 1%	Needles	195°
Ergotamine $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +194$ c = 1%	Needles	220°
Ergotamine $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +320$ (A) $[\alpha]_D^{20} = +420$ c = 1%	Needles (methyl alcohol) Prisms (alcohol, benzene, ethyl acetate)	228°
Ergotamine $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +306$ (A) $[\alpha]_D^{20} = +174$ c = 0.3%	Many sided tabular prisms (acetone)	165°-170°
Ergotamine $C_{20}H_{25}N_2O_5$	(A) $[\alpha]_D^{20} = +480$ (A) $[\alpha]_D^{20} = +366$ c = 0.575%	Long needles (methyl alcohol) Prisms (methyl acetate)	214°

and most important product is a compound having the formula  $C_{16}H_{16}N_2O_2$ , containing an indole nucleus, a double bond, a methylated nitrogen, and a carboxyl group. This substance has been called lysergic acid. Other products of hydrolysis are shown in Table 2.

Table 2

	Ergotamine Ergotamine	Ergotamine Ergotamine	Ergotamine Ergotamine	Ergotamine Ergotamine	Ergotamine Ergotamine
Lysergic acid.....	+	+	+	+	+
Ammonia.....	+	+	+	+	+
Hydroxyisopropylamine.....	+	+	+	+	+
d-Proline.....	+	+	+	+	+
1-Phenylalanine.....	+	+	+	+	+
1-Leucine.....	+	+	+	+	+
Methylpyruvic acid.....	+	+	+	+	+
Pyruvic acid.....	+	+	+	+	+

Only lysergic acid is common to all. Jacobs and Craig believe that

"lysergic acid is unquestionably the component of the alkaloids to which they owe their pharmacodynamic action."

Pharmacological studies of the ergot alkaloids are most extensive with respect to ergotamine, ergotamine, and ergonovine (ergometrine). Ergotamine and ergotamine are absorbed slowly from the gastrointestinal tract, ergonovine (ergometrine) quite rapidly. The most important effect after absorption is that on the smooth muscle, particularly that of the pregnant uterus. Here it increases both the tone and the rate and amplitude of the rhythmical contractions. This property is possessed most strongly by ergonovine (ergometrine). The effect on other smooth muscle mechanism resembles somewhat that of sympathetic stimulation. In the case of ergotamine, ergotamine, and ergosine, large doses are followed by a partial or complete paralysis of the response of sympathetically innervated structures to either sympathetic nerve stimulation or administration of epinephrine, particularly in those cases where the response is motor rather than inhibitory. Ergonovine does not possess this property. Administration of ergot or of its alkaloids to roosters results in a cyanosis and bluing of the comb. Large doses or repeated administration may result in development of gangrene of the tips of the comb and the tail of the white rat has also been produced experimentally with ergotamine. Gangrene of fingers or toes was a marked symptom of ergotism in the epidemics of poisoning. It has also followed excessive dosage with the alkaloid ergotamine clinically.

Assay of ergot prior to the dis-

covery of ergonovine (ergometrine) was largely biological, being based either on the ability to produce discoloration of the comb of the rooster (Leghorn cock, U.S.P. X, XI) or the ability to paralyze the response of strips of rabbit uterus to epinephrine (Broom-Clark method). A colorimetric method based on the van Urk reaction, did not differentiate between active and inactive isomers. The discovery of ergonovine and recognition of its importance has complicated the assay methods. Neither of the above mentioned makes possible a recognition of the amount of ergonovine present. Current attempts at development of assay methods are in the direction of determining the total alkaloids by a colorimetric method. Then the water soluble fraction is separated, and this fraction assayed either biologically or by a colorimetric procedure for ergonovine.

In clinical medicine the trend is definitely away from the use of ergot as such or in the form of the extract or fluidextract, and toward the employment of the pure alkaloids. In the U.S.P. XII ergonovine maleate and ergotamine tartrate are recognized. The first of these finds its use almost solely in obstetrics. The second has frequently been employed in the treatment of migraine, where its mode of action is as yet unexplained.

Many workers have contributed to chemical and pharmacological knowledge in this field in recent years. Among these may be mentioned the late George Barger, who not only contributed to the experimental work but whose two monographs on ergot form the major source of material for all other reviews; Arthur Stoll; S. Smith and G. M. Timmis; W. S. Jacobs and

L. C. Craig. The articles listed below will serve as an introduction to the literature of the subject.

<sup>1</sup> Barger, Geo.: Ergot and Ergotism. Gurney and Jackson, London, 1931.

<sup>2</sup> Barger, Geo.: The Alkaloids of Ergot. Heffter's Handb. der exper. Pharmacol., Ergänzwk. VI., Springer, Berlin, 1937.

<sup>3</sup> Stoll, A.: Les Alcaloïdes de l'Ergot de Seigle. Bull. Sci. Pharmacol., 43: 465, 1936.

<sup>4</sup> Smith, R. G.: The Present Status of Ergonovine. Rept. of Council on Pharmacy and Chemistry, J. Amer. Med. Assn., 111: 2201, 1938.

<sup>5</sup> Nelson, Erwin E. and Calvery, H. O.: Present Status of the Ergot Question. Physiol. Rev., 18: 297, 1938.

<sup>6</sup> Jacobs, Walter A.: The Chemistry of the Ergot Alkaloids. From: Chemical Kinetics and Natural Products, University of Pennsylvania Press, Philadelphia, 1941.

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## ERGOT ALKALOID TESTS

See Evers, Hering, Tanret, Tschirch.

## ERGOTAMINE

See Ergot.

## ERGOTAMININE

An alkaloid which melts at about 252° with decomposition and whose physiological action is similar to that of ergotamine.

## ERGOTHIONEINE

The betaine of thiohistidine found in blood and ergot; of unexplored biochemical function; may be involved through its sulfhydryl group in vitamin-reduction processes. See Ergot, Thioneine.

## ERGOTHIONEINE TEST

See Hunter.



**ERGOTININE**

See Ergot.

**ERGOTISM**

See Ergot.

**ERGOTOCIN**

Ergometrine.

See Ergot.

**ERGOTOXINE**

See Ergot.

**ERIODICYTOL**

A flavone, existing as a glycoside in vitamin P.

**ERUCIC ACID**

Unsaturated fatty acid,  $C_{22}H_{42}O_2$ , with one double bond, found in mustard seed and rapeseed oils; m.p.  $33-4^{\circ}C$ .

**ERGOTOTOXINE**

See Ergot.

**ERYTHEMA**

Redness of the skin; described as (1) simplex, (2) multiforme and (3) nodosum. Erythema simplex may be due to drugs, sun-burn, fevers, intestinal toxemias and includes blushing. Erythema multiforme is accompanied by exudations, macules, papules, vesicles, nodules and is of toxic origin which is endogenous as well as exogenous. It is related to urticaria and purpura. Erythema nodosum is frequent upon the legs and is attributed to exposure to cold and wet. It is excited by fever conditions and the like. Therapy is usually symptomatic for all forms, but vaccines sometimes help.

**ERYTHROBLAST**

Nucleated red blood cell, precursor of red blood corpuscle.

**ERYTHROCRUORINS**

Red respiratory chromoproteins of many invertebrates, which

closely resemble hemoglobin in their chemical nature.

Their hemin group appears to be protoheme throughout, but the protein components vary in structure and are different from globin. The molecular weights of the erythrocruorins vary between 16,500 and several million. As a rule, erythrocruorins, locked up in red blood cells, are low-molecular while those freely dissolved in the blood plasma are high-molecular.

**ERYTHROCYTES**

Red blood cells, comprising between 40-45% of the volume of blood. They are non-nucleated, circular, biconcave discs; about 8  $\mu$  in diameter, and containing about 34% by weight or  $3 \times 10^{-13}$  grams each of hemoglobin, by means of which they carry oxygen to the cells.

See Permeability.

**ERYTHRODEXTRIN**

An amylase hydrolysis product of starch.

**ERYTHROGRANULOSE**

Alpha amyloextrin produced by alpha amylase on starch.

**ERYTHROIDINE**

An alkaloid,  $C_{16}H_{19}NO_3$ , isolated from certain species of erythrina, and existing in two stereoisomeric forms; both forms have curare-like action.

**ERYTHRITOL**

A 4 carbon carbohydrate alcohol, found in lichens, m.p.  $125^{\circ}$ .

**ERYTHROPOIESIS**

The process of the production of red blood cells by the bone marrow.

**ERYTHROSE**

A 4 carbon-sugar,  $C_4H_8O_4$ , having d- and l-forms.

**ERYTHROZYME**

A hetero beta-glycosidase of madder; primeverosidase.

**ESCHATIN**

A commercial preparation of natural adrenal cortex hormone.

**ESCULETIN**

Aesculetin; 6,7-dihydroxycoumarin;  $C_9H_6O_4 \cdot H_2O$ ; the non-carbohydrate group of esculin.

**ESCULIN**

$C_{15}H_{16}O_8$  hydrate; aesculin; a glycoside of the bark of the horsechestnut, consisting of glucose and aesculetin; crystallizes as prisms from water or dilute alcohol; m.p.  $205^\circ$ . It is a febrifuge.

**ESERINE**

Physostigmine,  $C_{15}H_{21}O_2N_3$ , alkaloid of Calabar bean; used to contract pupil of eye, also for tetanus.

**ESOPHAGOSCOPY**

See Gastro-Enterology.

**ESOPHAGUS**

See Gastro-Enterology.

**ESSENTIAL HYPERTENSION**

See Hypertesia.

**ESSENTIAL OILS**

Odorous constituents of plants which steam distil. They find application in perfumery and medicine. They are hydrocarbon types, ester types, sulfides, etc. Compounds in plants, volatile with steam, extractable with hydrocarbon solvents. They include terpenes of the general formula  $C_{10}H_{16}$ , e.g. pinene, camphene, limonene; alcohols and ketones, e.g. camphor, menthol, borneol, menthone, cineol; a geraniol and citronellol group; benzene hydrocarbons like cymene and styrene; phenols like eugenol, thymol, carvacrol; acids and esters; aliphatic alcohols; aliphatic alde-

hydes; sulfides like allyl sulfide; organic bases like indol; and occasionally small amounts of paraffin hydrocarbons.

**ESTERASES**

A group of enzymes that hydrolyze esters. Sometimes the individual enzymes are named from the organ where they originate, as liver esterase; and sometimes the name indicates the product hydrolyzed, as sulfatase.

See also Enzymes, Non-Proteolytic.

**ESTRADIOL**

$C_{18}H_{24}O_2$ ; m.p.  $174^\circ C$ ; the natural female estrogenic hormone produced by the ovarian follicles. It controls the menstrual cycle, and to a large extent, the secondary sex characteristics.

**ESTRADIOL MONOBENZOATE**

m.p.  $195^\circ$ ; progynon B. The benzoyl ester of estradiol, usually at  $C_8$ , used clinically in treatment of menopause and disturbed estrus. Preferable to estradiol as the slow ester hydrolysis allows the use of larger and less frequent doses.

**ESTRIOL**

$C_{18}H_{24}O_3$ ; m.p.  $280^\circ$ ; an estrogenic hormone which can be dehydrated to estrone. It is much less active than estrone or estradiol.

**ESTROGENIC HORMONES**

A group of naturally occurring sterols which control the estrus cycle and secondary sex characteristics in the female. Those found in the human are estrone, estradiol and estriol, estradiol being the primary hormone secreted by the Graffian follicle; estrone being its waste product, and having only 1/10th its potency. In addition, three other weak

estrogenic hormones, equilin, hipulin and equilenin are found in equine urine. Excessively large doses in rats may cause cancer. See individual entries, Steroids.

See also Blood Sugar.

### ESTROGENS, METABOLIC EFFECTS OF

See Estrogens, Synthetic.

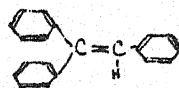
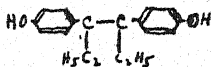
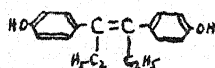
### ESTROGENS, ROLE IN PLANTS

See Plant Growth Hormones.

### ESTROGENS, SYNTHETIC

The term synthetic estrogen as

used in this review, includes those compounds which have estrogenic activity and yet lack the cyclopentenophenanthrene nucleus. This definition excludes derivatives of the natural estrogens from consideration, although strictly speaking, such a compound as ethinyl estradiol is a synthetic substance and does not occur as such in nature. The members of this group which have received the most attention are the following substances and certain derivatives of them: diethylstilbestrol, diethylhexestrol, and triphenyl ethylene.



In the four years since Dodds and his co-workers<sup>1</sup> first announced the synthesis and estrogenic potency of diethylstilbestrol, a large amount of research has been done in the field and an extensive bibliography has accumulated.

#### Assay

In the following table are listed some of the known synthetic estrogens. As in the case of the natural estrogens, these substances must be assayed biologically in order to establish their potency. This may be done by determining the amount necessary to produce a cornified vaginal smear or to produce an increase in the uterine weight of immature or spayed rats or mice. Most of the values listed were obtained by the vaginal smear method on spayed rats. Any biological assay should (1) employ enough animals to give the results statistical significance; (2) compare two substances of which one is a known standard; (3) compare substances

having certain pharmacological similarities such as in the rate of absorption or length of action. Unfortunately these criteria have not always been observed with estrogens and consequently, the assay data given in the table must be considered as tentative. The figures quoted merely show the general range of activity of the substances in producing an estrous smear. In some cases the length of action is indicated by the number of days the animal remains in estrus.

#### Relation Between Structure and Activity

Until the work of Dodds and his collaborators appeared, it was thought that the cyclopentenophenanthrene nucleus was an indispensable structure in an estrogenic compound. Dodds and Lawson<sup>2</sup> showed that the phenanthrene ring is not necessary. In fact, it is possible to obtain an estrous smear with a

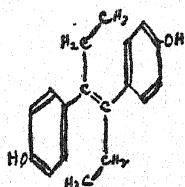
# DICTIONARY OF BIO-CHEMISTRY

Table 1.

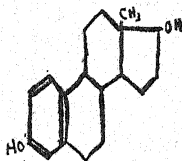
Compound	Dose mg.	Animals in Estrus %	Days in Estrus	Authority
Phenanthrene derivatives, as 1-Keto-1:2:3:4-tetrahydrophen- anthrene	100	100	20	(4)
Benzanthrane derivatives, as 9:10-Dihydroxy-9:10-di-n- propyl-9:10-dihydro-1:2:5:6- dibenzanthracene	0.1	60		(4)
Acenaphthene derivatives, as 1:2-Dihydroxy-1:2-di- $\alpha$ -naphthyl acenaphthene	1	20		(2)
Naphthene derivatives, as Diphenyl- $\alpha$ -naphthyl carbinol	100	100		(2)
Benzophenone derivatives, as 4:4'-Dihydroxy-benzophenone	100	80		(2)
Phenol derivatives, as 4-Propenyl phenol (anol)	100	100		(2)
Diphenyl derivatives, as 4:4'-Dihydroxy diphenyl	100	100		(2)
Diphenyl methane derivatives, as 4:4'-Dihydroxy- $\alpha$ : $\alpha$ -dimethyl diphenyl methane	100	100		(2)
Diphenyl ethane derivatives, as Stilbene	25	100		(2)
4-Hydroxy stilbene	5	40		(2)
Triphenyl ethylene	5	50		(2)
Triphenyl chloroethylene	0.1	100	12	(5)
$\alpha$ : $\alpha$ -Di-(p-ethoxyphenyl) $\beta$ -phenyl bromoethylene	0.1	100	93	(5)
4:4'-Dihydroxy- $\gamma$ : $\delta$ -diphenyl- $\alpha$ : $\delta$ -hexadiene	0.0004	70		(3)
4:4'-Dihydroxy- $\gamma$ : $\delta$ -diphenyl- $\beta$ : $\delta$ - n-hexane (Diethylhexestrol)	0.0001	20		(6)
Dihydroxy stilbene derivatives, as 4:4'-Dihydroxy stilbene	.5	80		(3)
4:4'-Dihydroxy- $\alpha$ -ethyl stilbene	0.1	50		(3)
4:4'-Dihydroxy- $\alpha$ : $\beta$ -dimethyl stilbene	0.02	80		(3)
4:4'-Dihydroxy- $\alpha$ : $\beta$ -diethyl stilbene (Diethylstilbestrol)	0.0003	80		(3)
4:4'-Dihydroxy- $\alpha$ : $\beta$ -di-n-propyl stilbene	0.01	75		(3)
Diethylstilbestrol derivatives, as Diethylstilbestrol	0.01		5	(3)
Diethylstilbestrol di-acetate	0.01		21	(3)
Diethylstilbestrol di-propionate	0.01		52	(3)
Diethylstilbestrol di-n-butyrate	0.01		4	(3)
Diethylstilbestrol di-methyl ether	1		144	(3)
Diethylstilbestrol mono-methyl ether	0.05		50	

substance as anol containing only one benzene ring. They found that certain compounds consisting of two phenol groups joined by a carbon chain show estrogenic activity which varies with the number of carbon atoms in the chain, the position of the double bonds and of substituent groups attached to the carbon chain. Observation of the table will indicate that many of the substances contain a phenolic hydroxyl in a position para to some other group. Aromatic compounds lacking the hydroxyl group may perhaps be active through their ability to form such a compound in

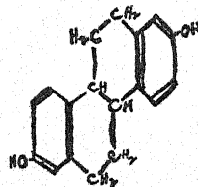
the body. For example stilbene, which requires 25 mg. to produce estrus, is oxidized in the rabbit to 4:4'-dihydroxystilbene, which requires only 5 mg. to produce estrus. It is possible (but not proved) that a similar oxidation occurs with other substances such as triphenyl ethylene. Dodds et al<sup>1</sup> have pointed out that when diethylstilbestrol is depicted as shown below, it bears a resemblance to the natural estrogens. However the closer similarity produced by ring closure (dihydroxyhexahydrochrysene) is accompanied by a loss of estrogenic activity.



Diethylstilbestrol



Estradiol



Dihydroxyhexahydrochrysene

An interesting study of the activity of an homologous series is shown in the stilbenediol series with alkyl substitutions on the ethylenic carbons.<sup>3</sup> Maximum activity is obtained with diethyl substitution, chains longer or shorter than C<sub>2</sub> having much less activity (see Table 1). Similarly, in the case of members of the dihydroxy diphenyl methane series, maximum activity is obtained when the intermediary carbons total six, producing a compound similar to diethylhexestrol as regards the intermediary carbons. Esterification of the phenolic hydroxyl, as with the natural estrogens, produces somewhat weaker compounds, but, as shown in the table, they have a more prolonged action. In the diethylstilbestrol ester series, the dipropionate is outstanding. Methylation of the hy-

droxyl groups of diethylstilbestrol produces a compound with especially long action. The cis-isomer of diethylstilbestrol is much weaker than the trans.

#### Biological Action in Experimental Animals

Except in a few minor details, the synthetic estrogens seem to produce to a remarkable extent the same qualitative changes in animals as do the natural estrogens. To use a convenient term introduced by Parkes, these substances are "gynecogenic" as well as estrogenic; that is, besides producing an estrous smear, they act on other tissues in a manner similar to the natural female sex hormones. Ample evidence of the essential similarity in the effect of these substances now exists. Small doses of diethylstil-

bestrol produce thickening and cornification of the vaginal epithelium of rodents and higher animals, growth and increase in weight of the uterus, sensitization of the uterus to the action of progesterone, and in some animals growth of the mammary gland duct system and nipples. In rats larger doses, in addition, cause cessation of growth and a decrease in body weight, atrophy of the ovaries, testes, prostate and seminal vesicles, and an increase in weight of the pituitary and in some cases of the adrenals. Diethylstilbestrol has been most studied in these respects, but such gynecogenic effects have also been produced by diethylhexestrol and the triphenyl ethylene series. The most outstanding distinction between the behavior of the synthetic and natural estrogens lies in the fact that the synthetic substances lose very little activity when they are administered orally.

Recent studies indicate that estrogens including diethylstilbestrol have certain metabolic effects which formerly received little attention. Calcium metabolism is influenced by estrogen administration. In rats, mice, and especially in birds, estrogens produce a rise in blood calcium which is apparently followed by closure of the epiphyseal lines and osteoblastic proliferation in the marrow cavity of the long bones. Diethylstilbestrol also has been found to have these effects in so far as they have been investigated. Similarly, in regard to fat metabolism, diethylstilbestrol resembles the lipemia in birds. The relation of estrogenic substances to carbohydrate metabolism is somewhat more controversial. Carbohydrate levels seem to be raised in rats by diethylstilbestrol and other estrogens.

Muscle glycogen is not affected, but the blood sugar level tends to rise somewhat, while liver glycogen is considerably raised if the period of estrogen administration is prolonged.<sup>7</sup> In some cases glycogen is stored in the liver to such an extent as to produce an unusual microscopic appearance of the hepatic cells.<sup>8</sup> The mechanism of the glycogen storage effect does not seem to be direct. Thus estrogens also increase the insulin content of the pancreas,<sup>9</sup> and since neither this effect nor the increase in liver glycogen is evident in hypophysectomized animals,<sup>10</sup> it would seem that the action of estrogens in elevating liver glycogen takes place through an action on the anterior pituitary. However, the adrenal cortex may play a role in this response. Histological changes in the adrenals are well-known after estrogen administration and liver glycogen is not increased after diethylstilbestrol in adrenalectomized rats. The situation is further complicated by the observation that estrogens have a diabetogenic effect in some animals, while there are some clinical reports of diabetes mellitus being alleviated by estrogens. On the contrary, other clinical studies have shown little effect from estrogens, and diethylstilbestrol apparently does not affect experimental canine diabetes mellitus.

### Toxicity

The first experimental studies on the effect of large doses of diethylstilbestrol led to the conception that the substance was potentially dangerous because it produced degenerative changes in the liver.<sup>11</sup> Furthermore, the nausea and vomiting which is commonly encountered in the clinical administration of the drug demanded added caution in its



use. Recently, the trend of experimental work has indicated that the histologic changes in organs resulting from large doses of synthetic estrogens are not alarming and, in fact, are similar to those produced by natural estrogens when given in sufficiently large amounts. The administration of estrogens in the rat produces vacuolization of the hepatic cells which is due to glycogen deposition and not to a degenerative change.<sup>8</sup> The adrenals are affected in some cases by a change which Cramer and Horning have called "brown degeneration," but the significance of this change is still not clear. In the dog a marked depression of hematopoiesis occurs with estrogens; however, this effect apparently does not take place in human beings. None of the anatomical changes found in experimental animals can account for the nausea and vomiting seen clinically and it is likely that these phenomena are of central origin. Results of liver function tests on patients receiving diethylstilbestrol have usually been within the normal range.

In clinical experiences with synthetic estrogens nausea, vomiting, abdominal distress, anorexia, lassitude and vertigo are of frequent occurrence, especially when comparatively large doses are administered.<sup>12</sup> Other toxic effects less commonly encountered have been diarrhea, rashes, paresthesia, and psychotic episodes.

In certain animals, estrogen administration over a long period of time will produce neoplasms. These results, first seen with the natural estrogens, have often been reproduced with diethylstilbestrol. Thus mammary adenocarcinoma can easily be produced in some strains of mice. Chromophobe adenoma of

the anterior pituitary is seen in some mice and rats, and fibromata in guinea pigs have been observed to follow injections of diethylstilbestrol.

### Metabolism

Little is known at the present time concerning the absorption, distribution and fate of the synthetic estrogens. Stroud<sup>13</sup> injected rabbits with diethylstilbestrol, diethylhexoestrol, and dihydroxydiphenylhexadiene and was able to isolate the free phenol in each case from the urine. He also obtained the free phenol after hydrolysis of the "combined" urinary fraction, indicating that conjugation of the estrogens had occurred. Of a total of 3 gm. of diethylstilbestrol injected, 25.2% was recovered in the urine, 14.2% free and 11.0% combined. These figures are probably low, since 30% of injected diethylstilbestrol has been isolated from rabbit urine in a conjugated form, identified as a monoglycuronide of diethylstilbestrol.<sup>14</sup> Apparently the substance undergoes little destruction in the body, conjugation with glycuronic acid being the only known manner in which it is metabolized. This change probably takes place in the liver. The synthetic estrogens thus stand in marked contrast to the natural estrogens as regards their metabolism since the natural estrogens are largely oxidized in the body and only a small fraction is excreted in the urine.

### Clinical Aspects

Since its introduction, diethylstilbestrol has been subjected to extensive clinical trial as an oral substitute for the natural hormones in estrogenic therapy. Most studies have been directed to its use in the symptoms of the menopausal syn-

drome. It is an effective agent in this respect. It is much cheaper than the natural estrogens and loses little potency when given by mouth, but it has the disadvantage of giving rise to unpleasant side actions which are discussed above. Diethylstilbestrol monomethyl ether, diethylhexestrol, and triphenylchloroethylene are also being subjected to clinical investigation at this time.

These substances are also given in other conditions in which estrogenic therapy has been used. Diethylstilbestrol has proved to be of value in treating cases of senile vaginitis, leukoplakia vulvae, some cases of secondary amenorrhea, functional uterine bleeding and dysmenorrhea. It has apparently been successfully used in the suppression of lactation.

#### Problems for Future Research

In view of the fact that the field of synthetic estrogens is so new, it is not surprising that many unanswered questions have been provoked. The introduction of the synthetic substances has also stimulated further thought concerning the natural estrogens. The question of the relation of chemical structure to biological activity in estrogens has been reopened. For a more complete understanding of the synthetic estrogens a thorough study of the pharmacology and metabolism of these substances is called for. Many unsolved problems are concerned with the metabolic effect of estrogens, the elucidation of their relation to carbohydrate metabolism being outstanding. There is always present the all-important task of impartial clinical evaluation of the substances. Finally, there remains the objective of producing an estrogen active by mouth, lacking the

unpleasant side-actions of diethylstilbestrol.

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#### BIBLIOGRAPHY

- <sup>1</sup> Dobbs, Goldberg, Lawson, and Robinson: *Nature*, 141: 247, 1938.
- <sup>2</sup> Dodds and Lawson: *Proc. Roy. Soc. London*, B125: 222, 1938.
- <sup>3</sup> Dodds, Goldberg, Lawson and Robinson: *Proc. Roy. Soc. London*, B127, 140, 1939.
- <sup>4</sup> Cook, Dodds, Hewett and Lawson: *Proc. Roy. Soc. London*, B114: 272, 1934.
- <sup>5</sup> Robson and Schönberg: *Nature*, 150: 22, 1942.
- <sup>6</sup> Campbell, Dodds, Lawson and Noble: *Lancet*, 2: 312, 1939.
- <sup>7</sup> Janes and Nelson: *Am. J. Physiol.*, 136: 136, 1942.
- <sup>8</sup> Teague: *J. Pharmacol. & Exper. Therap.*, 75: 145, 1942.
- <sup>9</sup> Griffiths, Marks and Young: *Nature*, 147: 359, 1941.
- <sup>10</sup> Fraenkel-Conrat, Herring, Simpson and Evans: *Proc. Soc. Exper. Biol. & Med.*, 48: 333, 1941.
- <sup>11</sup> Loeser: *Klin. Wchnschr.*, 18: 346, 1939.
- <sup>12</sup> Shorr, Robinson and Papanicolaou: *J. A. M. A.*, 113: 2312, 1939.
- <sup>13</sup> Stroud: *J. Endocrin.*, 1: 201, 1939.
- <sup>14</sup> Mazur and Shorr: *J. Biol. Chem.*, 144: 283, 1942.

#### ESTRONE

$C_{18}H_{22}O_2$ ; m.p. 256-259°; a female sex hormone, found in pregnancy urine and stallion urine, probably as a waste product of primary hormones. Produces estrus and controls secondary sex characteristics. 10,000,000 I.U./gm.

#### ETHOCAINE

See Procaine.

#### ETHYL BUTYRATE TEST FOR PANCREATIC LIPASE

When litmus is added to a mix-

ture of test solution and a neutral aqueous solution of ethyl butyrate a red color is obtained.

# ETHYLENE RIPENING

See Agricultural Biochemistry.

# ETHYLENESUCCINIC ACID

See Succinic Acid.

# ETHYL SULFIDE TEST

See Liebermann.

# ETIOLATION

The pale yellow appearance of a plant grown without light, due to a chlorophyll precursor.

# ETIOLIN

Yellow plant chlorophyll precursor pigment.

# EUBACTERIALES

See Microbiology.

# EUCALYPTUS OIL

A distillate of the leaves of *Eucalyptus* species, chiefly cineole.

# EU-COLLOIDS

Colloids whose colloid-particles are identical with single molecules of a substance; if many molecules coalesce the colloids are "association colloids."

# EUCORTONE

See Cortin.

# EUCUPINE

An alkaloid, isoamyl-hydrocupreine, which is used in the form of the dihydrochloride as a powerful bactericide and local anesthetic; also used internally in malaria, sepsis and influenza; externally to relieve pain in carcinoma, X-ray burns, hemorrhoids.

# EUGENOL

4-allyl-2-methoxyphenol, found in oil of cloves, bay and cinnamon; a strong antiseptic used in dentistry.

# EUGLENARHODON

See Carotenoids.

# EUGLOBULIN

A globulin found in the blood serum. Unlike pseudoglobulin it contains phosphorus, is insoluble in water, soluble in dilute salt solutions, and is precipitated by  $\frac{1}{4}$  saturated ammonium sulfate.

# EURYHALINE

A term applied to animals that can withstand large changes in external salinity, e.g. shore crab *Carcinus*; opposite of stenohaline.

# EUSTACHIAN TUBE

Passage joining middle ear to throat for pressure equalisation.

# EVERS REACTIONS FOR

# ERGOT ALKALOIDS

A solution of ground ergot in glacial acetic acid is extracted with ether, the ether evaporated and the residue treated with an equal volume of 50% sulfuric acid. Careful mixing of the two layers gives rise to a violet-blue color.

Reference: Pharm. J. 118, 721 (1927).

# EVIPAN

Methyl-cyclo-hexenyl-N-methyl-barbituric acid, a hypnotic causing general anaesthesia, requiring great care in use.

# EVOCATOR

An organizer hormone present in the egg, liberated at the "organizer center" (dorsal lip of the blastophore); comes from an inactive precursor; essentially the chemical stimulus for neuralization.

# EVOLUTION, CHEMICAL

See Biochemistry (Definitions).

# EWALD MEAL

2 slices of toast and 8 oz. water or their equivalents, used in testing power of the fasting stomach to secrete HCl, etc.

**EXCELSIN**

A crystalline globulin of the Brazil nut.

**EXERCISE**

Under this head one might include the multitude of conditions relevant to muscular development. The physiologists have made their contributions concerning the complex adjustments during and following exercise in the respiration, circulation, and with the biochemists, in the composition of the blood and the tissues, in kidney function and in the nervous system, the endocrines, and in reaction to foreign substances which may be stimulants or depressants. The most commonly known fact is that of physiological albuminuria following violent exercise. Bicarbonate combats this condition. Occasionally there is also glycosuria after exercise. Though carbohydrates are essential they are not entirely irreplaceable as fuel for hard work. Biochemically "second wind" is increased oxygen intake along with related changes. Much has been made of the effect of hormones, which however need a great deal more of study. The effect of estrogens is very marked in catalyzing activity of mice and other animals running in cages. Sick patients are often helped by either male or female sex hormones. Special foods have been prepared for athletes and vitamins have been praised, possibly because they improve the general health. Emphasis on vitamin C<sub>1</sub> however, is well indicated. Physostigmine is an instance of a "dope" which brings out extra activity for which the penalty may be paid later. Allergy to muscular work has been mentioned as identifiable by "hives" or asthma after exercise.

Reference: A. H. Steinhaus, Annual Review of Physiology IV, 695-716 (1941).

**EXOCRINE GLAND**

Gland supplied with duct.

**EXO-ENZYME SYSTEM  
HYDROLYSIS**

See Cellulose Decomposition.

**EXOGAMY**

Outbreeding.

**EXOPEPTIDASE**

See Peptidase.

**EXOPHTHALMIC GOITER**

See Goiter.

**EXOPHTHALMOS**

See Goiter.

**EXOPLASM**

Ectoplasm.

**EXOSKELETON**

Endoskeleton; dermoskeleton; external skeleton of invertebrates.

**EXOSMOSIS**

Passage of fluid outwardly through membranes.

**EXOTHERMIC**

Liberating heat (applied to systems or isolated reactions).

**EXOTOXINS**

See Microbiology, Immunological Phenomena.

**EXTERNAL SECRETIONS**

They are: milk, sebaceous secretions, mucous secretions.

**EXTEROCEPTOR**

Nerve receptor dealing with stimuli from outside.

**EXTON REAGENTS FOR  
ALBUMIN IN URINE**

I. A turbidity or precipitate is obtained when the urine is treated with a solution of 5 gm. sulfosalicylic acid and 20 gm. sodium sulfate in 100 cc.

II. One liter of a filtered solution of 50 gm. sulfosalicylic acid, 10 gm. sodium sulfate, 25 cc. of 0.4% aqueous solution of bromphenol blue may be used for the quantitative estimation of albumin.

Reference: J. A. M. A. 80, 529 (1923); 85, 388 (1925). J. Lab. Clin. Med. 10, 695 (1925).

## EXUDATE

The readily coagulable filtrate of blood through capillaries, when an inflammatory process is involved.

## EYE, BIOCHEMISTRY OF

One may speak of "chemical ophthalmology" as a possible division of chemical biology dealing with the chemical aspects of the entire evolution and functioning of eye tissues. The tissues of the eye resemble other tissues of the body and contain proteins much like the rest of the body with special characteristics now and then, e.g. the albuminoid of the lens substance. Keratin has not been discovered, but neurokeratin has been found. Protamines and histones have not been looked for. Many lipids have been found and there is a full quota of carbohydrates and glycogen. Many nitrogen compounds and enzymes have been reported. The inorganic constituents are distributed in an interrelated manner.

Special adaptations are characteristic of the cornea, lens and vitreous humor: obtaining of oxygen partly from the air by the cornea, peripheral growth of the lens, which is without nerve and blood supply, the gel character of the vitreous humor. The role of visual purple in the rod-shaped cells of the retina is unique. The eyes are involved in diseases like xanthomatosis, xerophthalmia, night blindness and the dermatitis of avitaminosis B<sub>1</sub>, cataract formation and glaucoma.

Divisions of the subject are: chemistry of the external secretions, chemistry of the conjunctiva, of the sclera, of the cornea, of the uveal tract (iris, ciliary body and choroid), of the retina, of the aqueous humor, of the vitreous humor, and of the lens. Chemical analyses have been made in the entire field, e.g. of tears showing many constituents including cholesterol, immunologically active proteins, enzymes, a bacteriolytic substance, lysozyme, and the like.

Reference: A. C. Krause, The Biochemistry of the Eye, Johns Hopkins Press.

## EYELID (THIRD)

Nictitating membrane, well developed in birds.

## F

### FABINYI REACTION FOR ACETONE

0.25 cc. of acetone are treated with 4 cc. N sodium hydroxide and 1 gm. of salicylaldehyde, shaken thoroughly and allowed to stand for 15 minutes. The product formed gives a red color with alkalis.

Reference: Münch. med. Wochschr. 1905, 628. J. Lab. Clin. Med. 13, 1155 (1928).

### FACTOR, SPREADING

See Microbiology.

### FACTOR I

Vitamin B<sub>6</sub>.

### FACTOR V

A factor necessary for the growth of certain haemophilic organisms, probably like Euler's cozymase or Warburg's coenzyme.

### FACTOR W

A thermolabile factor necessary for rat growth found in liver, yeast and milk.

### FACTOR Y

See Pyridoxine.

### FALLING SICKNESS

See Epilepsy.

### FALLOPIAN TUBE

Upper part of passage for ovum in mammals.

### FARINA

Potato starch.

### FARNESOL

Sesquiterpene alcohol found in many essential oils, used in perfumes.

### FASCIA

Ensheathing, connecting tissue about a part.

### FASTING METABOLISM

Basal metabolism.

### FAT, FORMATION FROM CARBOHYDRATE

See Carbohydrate Metabolism.

### FAT HYDROLYSIS

See Twitchell Reagent.

### FAT METABOLISM

See Carbohydrate and Fat Catabolism.

### FAT (NEUTRAL FAT)

Triglyceride of a fatty acid.

### FAT REAGENT

See Valenta.

### FATS

Esters of glycerol with three molecules of fatty acid. Fats are found in both the plant and animal kingdom, in the latter acting as supporting and protective tissue, and as a secondary source of energy. They are soluble in ether, CHCl<sub>3</sub>, CS<sub>2</sub>, etc., but sparingly soluble in ethyl alcohol.

### FAT-SPARING

The action of sugar in preventing a flooding with fat which accompanies a ketosis or acidosis or a



general carbohydrate failure of energy.

# FAT TRANSPORT

See Carbohydrate and Fat Catabolism.

# FATTY ACID

Monobasic aliphatic acid. Some restrict the usage to saturated acids. Cyclic acids such as chaulmoogric acid are sometimes termed fatty acids when they occur naturally as constituents of fats.

# FATTY ACID CATABOLISM

See Carbohydrate and Fat Catabolism.

# FATTY ACIDS, OXIDATION OF

See Carbohydrate and Fat Catabolism.

# FAUCES

(1) passage between mouth and pharynx; (2) mouth of a spiral shell.

# FAUGHT TEST FOR ACETONE

5 cc. of test solution are mixed with a solution of 0.06 gm. sodium nitroprusside in 5 cc. distilled water and 5 drops of a 10% ethylenediamine hydrate solution are floated on this; acetone is indicated by a pink or red zone (no turbidity). Sensitivity—1:100000.

Reference: Faught, *Essentials of Laboratory Diagnosis*. Am. J. Pharm. 98, 643 (1926).

# FEAR, EFFECTS OF

See Psychiatry, Biochemistry of.

# FEARON TEST FOR VITAMIN A

In the presence of pyrogallol, trichloroacetic acid and an oxidizing agent vitamin A gives a pink coloration.

Reference: *Biochem. J.* 19, 888 (1925); 20, 869 (1926). *Lancet* 1926, II, 806.

# FEATHERS

See Hair.

# FECHNER'S LAW

The increase of intensity of sensation with the logarithm of the stimulus for moderate values above the threshold of sensation.

# FECUNDATION

Fertilization impregnation.

# FEHLING REAGENT FOR GLUCOSE

Solution A—34.64 gm. copper sulfate dissolved in water and diluted to 500 cc. Solution B—173 gm. Rochelle salt mixed with 150 cc. potassium hydroxide (sp. gr. 1.14) and diluted with water to 500 cc. Equal volumes of A and B are mixed previous to use.

Red cuprous oxide precipitates when glucose is boiled with the solution. One cc. reagent is equivalent to 5 mg. glucose. Sensitivity—1:5000.

Reference: *Ann.* 72, 106 (1849); 75, 106 (1858). *Pharm. Zentr. Halle* 1854, 936. *Zeit. anal. Chem.* 7, 490 (1870). *Repert. de Pharm.* 1900, 74. *J. Physiol.* 1902, 156. *Chem. Weekblad* 1, 12 (1903). *Bull. soc. chim.* 35, 1285 (1906). *Deut. med. Wochschr.* 1907, 427. *J.A.M.A.* 1907, No. 4.

# FENCHONE

$C_{10}H_{16}O$ ; d-form found in fennel and lavender oils, l-form in thuja oil; dicyclic ketone, m.p. 5°, b.p. 192°.

# FENNEL

Dried ripe fruits of *Foeniculum vulgare*, constituent of compound licorice powder, an aperient; contains fenchone.

# FENTON TEST FOR HEXOSES IN URINE

A paste is formed by adding anhydrous calcium chloride to 4 cc. urine and boiled a few minutes

with 10 cc. toluene and a few drops of phosphorus trichloride. The solution is cooled, after decanting the toluene, and treated with 1 cc. ethyl malonate and a little alcohol, and potassium hydroxide solution added dropwise. A rose-red color forms. A blue fluorescence is obtained when the solution is diluted with water or alcohol. Pentoses do not react.

Reference: Lancet 1907, 215, 172.

#### **FERAL**

Reverting to wild form after cultivation.

#### **FERMENTATION**

See Microbiology.

#### **FERRIC CHLORIDE TEST**

A test for thiocyanates in saliva.

#### **FERRICYTOCHROME**

The combination of ferric ion with cytochrome.

#### **FERRIPROTOPORPHYRIN**

See Hematin.

#### **FERROCYTOCHROME**

The combination of ferrous iron with cytochrome, the reduction product of ferricytochrome.

#### **FERROPROTOPORPHYRIN**

See Haem.

#### **FERTILIZATION**

Fecundation; union of sex cells to form a zygote; the process which stimulates cleavage and development of the ovum; generally effected by entrance of a spermatozoan into the ovum.

#### **FERTILIZER**

See Agricultural Biochemistry.

#### **FERTILIZIN**

A substance claimed to be present in unfertilized eggs serving to attract sperm. (obs)

#### **FEVER, ESTIVO-AUTUMNAL**

See Malaria.

#### **FEVER, INTERMITTENT**

See Malaria.

#### **FEVER, QUARTAN**

See Malaria.

#### **FEVER, REMITTENT**

See Malaria.

#### **FEVER, TERTIAN**

See Malaria.

#### **FEVER THERAPY**

Inductopyrexia; fever produced by electro-magnetic waves or equivalent means. The diseases treated typically are neurosyphilis, arthritis, gonorrhea, undulant fever, rheumatic fever, osteomyelitis, multiple sclerosis, allergy, optic atrophy and edema of the retina. Sulfanilamide is also used simultaneously. The outstanding successes have been in gonorrhea and neurosyphilis. The environment temperature in fever therapy is about 110° F. at a very high degree of humidity (in a cabinet). Body temperatures of 107° F. can be sustained for 3 hours. Pulse rates come up to as high as 120.

#### **FIBER PROTEINS**

See Protein Structure.

#### **FIBRIN**

The insoluble clotted material formed when thrombin or other material precipitates fibrinogen from the blood.

#### **FIBRINOGEN**

A soluble globulin found in the plasma. It forms insoluble fibrin under a number of conditions, such as hemorrhage, tissue injury, or exposure to oxygen. It is essential to blood clotting (see Clotting) and to repair of inflamed or damaged tissue.

#### **FIBRINOLYSINS**

See Microbiology.

#### **FIBROIN**

A scleroprotein found in silk; yields much glycine and alanine.

**FIBROIN, SILK**

See Protein Structure.

**FIBROPLASIA**

See Wound Healing.

**FIBULA**

Outer bone of leg.

**FICHTELITE**

$C_{19}H_{34}$ ; m.p.  $46.5^{\circ}$ ; a highly stable saturated dimethyl isopropyl anthracene, found in peat and lignite.

**FICIN**

The proteolytic enzyme of *Ficus* latex, inactivated by oxidizing agents and reactivated by cysteine.

**FIELD, GRADIENT**

A field in physics means a distribution of some non-material characteristic, such as force or energy, throughout portions of space unoccupied by material particles, but capable of interacting with such particles; an example is the electromagnetic field as treated by Maxwell.

The term has been broadened, especially in biological usage, to denote a spatial distribution of any characteristic, including the concentration of material particles or the rate of a chemical reaction. In this form it is virtually identical with the mathematical concept: "function of spatial coordinates."

That is: "There is a field of such-and-such in the chick embryo" means: "At every point of this embryo, the value of the characteristic 'such-and-such' is known or can be determined."

A caution is in order. The word "field" is frequently misused by using it in conjunction with a word which does not express a definite characteristic. In that case, the word is merely an elaborate circum-

locution for ignorance. To say, "In the chick embryo there is a differentiation field" means simply, "At every point of this embryo a process whose nature I do not know is going on."

An associated concept is "gradient." Mathematically this is the value, at any given point of space, of the rate of change of a spatial function in the direction of its most rapid change; in a one-dimensional function it is the same as the slope.

In biological usage the term has come to have a more qualitative meaning: the existence of variation of a characteristic throughout a region of space (usually a region of a living organism), the variation being unidirectional (i.e., increase or decrease). An example is the "axial gradient" of Child. Thus, to say that a certain Planarian shows an axial gradient means that some characteristic either steadily increases or steadily decreases as one passes from head to tail.

Consult "Principles of Development," by Paul Weiss, and "Experimental Embryology," by J. Huxley and G. DeBeer, for the biological usage of "field" and "gradient," as well as examples.

For use of field in physics, see "Foundations of Physics," by Lindsay and Margenau.

For "gradient" in mathematical sense, see any text of vector analysis.

JOHN M. REINER

**FILIAL GENERATIONS**

Symbols for offspring in Mendelian heredity,  $F_1$ ,  $F_2$ , etc.

**FILIFORM**

Capillary, thread like.

**FILOMUSI—GUELFITEST FOR DIFFERENTIATING HUMAN AND ANIMAL BLOOD**

Animal blood yields characteristic crystals with a 2% sodium fluoride solution; dog blood gives acicular and rabbit blood tetrahedral crystals. Human blood does not form crystals.

Reference: Zeit. Untersuch. Nahr.-u. Genussm. 2, 509 (1876).

**FILTERABLE VIRUS**

An infectious, disease-producing agent, usually smaller in size than most bacteria and larger than most protein molecules. The introduction of a virus within the living cells of a susceptible host is followed by the production of more of the same virus. Multiplication occurs only within living cells and may be accompanied by mutation with the formation of a new virus strain. Some viruses have been isolated in the form of crystallizable high molecular weight nucleoproteins — others appear to be about as complex as bacteria. (Stanley).

**FILTRATE**

Solution separated by filtration.

**FILTRATE FACTOR**

A member of the vitamin B complex found in yeast that prevents a nutritional dermatitis in the chick.

**FISCHER-FISCHL REACTION FOR GLUTATHIONE IN THE LENS OF THE EYE**

When the lens is soaked in 0.5M sodium or potassium cyanide for 8-18 hours, the nucleus and cortex are colored reddish-violet, the subepithelial protein layer is colorless, and the solution becomes yellow. The reddish color, due to glutathione, disappears upon acidification and is not given by glycocholic or glutamic acid.

Reference: Klin. Wochschr. 13, 285 (1934).

**FISCHER-HUPPMANN TEST FOR INDICAN IN URINE**

The test sample is mixed with an equal volume of basic lead acetate solution and filtered; 10 cc. of filtrate are treated with 10 cc. of a saturated glacial acetic acid solution of acenaphthenequinone and 2 cc. concentrated hydrochloric acid. After heating to boiling, 10 cc. hexahydrotoluene are added; a red color is obtained.

Reference: Pharm. Ztg. 76, 810 (1931).

**FISCHER REACTION FOR ALANINE AND PHENYLALANINE**

An odor of phenylacetaldehyde is evolved when 0.02 gm. phenylalanine are dissolved in 2-3 cc. 25% sulfuric acid, a small crystal of potassium dichromate added and the solution heated to boiling. When a solution of alanine in 25% sulfuric acid is treated with a small crystal of potassium permanganate and boiled, acetaldehyde is given off.

Reference: Zeit. physiol. Chem. 33, 174 (1901).

**FISSETIN**

3, 7, 3, 4-tetrahydroxyflavone, the coloring matter of the Rhus species, m.p. 330°.

**FISH-LICE**

Crustacean parasites found on skin and gills of fishes.

**FISSION**

Reproduction of a cell by splitting into two or more cells; cell-cleavage; schizogenesis.

**FISTULA**

Narrow passage leading from an abscess to the exterior.

### FISTULA, BILIARY

Arises spontaneously and as a result of injury. The spontaneous fistulae are probably always the result of inflammatory or malignant ulceration which establishes an abnormal passage between the biliary tract and some other organ or which leads to an outpouring of bile through an external opening in the abdominal wall.

### FISTULA, DUODENAL

Most frequently due to the ulceration of a stone through the wall of the gall bladder. Fistulae between the common duct and duodenum also occur.

### FISTULA, GASTRIC

There are no particularly characteristic symptoms of this type of fistula. Occasionally, however, gall stones have been vomited, and in such cases the inference is strongly suggestive that the fistula is gastric, although it is possible that also in a high duodenal fistula there might be vomiting of calculi.

### FISTULA, MUCOUS

Occurs sometimes after the operation of cholecystostomy. In this condition there is a discharge of thin, stringy, almost transparent mucus without bile.

### FIXED ACID

See Total Mineral Anionogens.

### FIXED BASE

See Total Base.

### FLAVIANIC ACID

2,4-dinitronaphthol-7-sulfonic acid, used in the purification and characterization of organic bases, e.g. acetylcholine, choline, creatinine, ethanolamine, guanidine, tyramine, urea, etc.

### FLAVIANIC ACID TEST

See Langley-Albrecht.

### FLAVINS

A group of yellow pigments, including Vitamin G and Warburg's yellow respirative enzyme widely distributed in nature, showing a strong fluorescence. They all have the iso alloxazine nucleus.

### FLAVONE

Benz-2-phenyl-alpha pyrone; the parent substance of many of the yellow plant pigments.

### FLAVONE GLYCOSIDES

Glycosides, principally of glucose or rhamnose, including apiin, acaiin, diosmin, lotusin, orobosin.

### FLAVONES

The name given to the class of yellow plant pigments derived from flavone.

They are also called xanthonenes or anthoxanthonenes and may be regarded as phenyl derivatives of the 1,4-pyrone nucleus. Representatives are: quercetin, morin, brazilin, hematoxylin, gentisin.

See individual entries.

### FLAVONOL GLYCOSIDES

Include datisein, fustin, galangin, kaempferitrin, quercitrin, quercetin, quercimeritrin, serotin, incarnatin.

### FLAVOPROTEIN

The flavin enzyme containing part which is cytoflav or lactoflavin-5-phosphoric acid and a protein; molecular weight about 80,000; reduced form oxidized by cytochrome-c.

### FLAVOPROTEIN ENZYMES

Flavin and protein containing enzymes which catalyze the oxidation of pyridine nucleotides and other substrates; can be resolved reversibly to lactoflavinphosphate and protein; include yeast I, yeast II, amino-acid oxidase (kidney) xanthine oxidase (milk) and

fumaric hydrase (yeast), named after men or source.

# **FLEMING REACTION FOR CYSTEINE**

0.5 cc. of a solution of 0.2 gm. of dimethyl-p-phenylene diamine in 100 cc. water are mixed with 1 cc. of test solution and treated with 1 drop 5% ferric chloride solution; a deep blue color, similar to methylene blue is obtained. The color may be salted out with sodium or zinc chloride.

Reference: Biochem. J. 24. 965 (1930).

# **FLEXNER ORGANISM**

See Gastro-enterology.

# **FLORIGEN**

See Plant Growth Hormones.

# **FLOUR, BLEACHED, TEST FOR**

See Shaw.

# **FLOUR, TEST FOR ALUMIN**

See Bell.

# **FLUORESCENCE**

The reemission of radiant energy at a longer wavelength than that of the illumination.

# **FLUORESCENCE BY CHLOROPHYLL**

See Photosynthesis.

# **FLUORINE METABOLISM**

See Teeth, Biochemistry of.

# **FLUOROSCOPY**

See Gastro-Enterology.

# **FLUOROSIS**

Disease due to excess of fluorine, known as mottled enamel of teeth in people.

# **FETUS**

The pre-natal stage succeeding the embryonic (in man the 7th) week and after.

# **FOLDED POLYPEPTIDE MOLECULES**

See Protoplasm.

# **FOLIC ACID**

A vitamin-like substance from spinach and other leaves, which may be released from all animal tissues by autolysis. It promotes yeast growth and bacterial growth.

Reference: Mitchell, H. K., Snell, E. E. and Williams, R. J., Jour. Am. Chem. Soc. 63: 2284 (1941).

# **FOLIN AND DENIS REACTION (1912)**

A test for the phenol nucleus, which is also used for tyrosine. When a solution of a compound made by boiling phosphoric acid, phosphomolybdic acid and sodium tungstate together, is added to a solution of tyrosine, and then sodium carbonate is added to the point of alkalinity, a blue color results.

# **FOLIN-DENIS COLORIMETRIC DETERMINATION OF TYROSINE IN PROTEINS**

The standard solution is prepared by solution of 0.001 gm. tyrosine in 25 cc. sodium carbonate solution and 5 cc. of the author's phenol reagent. The determination is made by heating 1 gm. of protein with 25 cc. 20% hydrochloric acid for 12 hours, diluting with water to 100 cc., adding 5 cc. of reagent to 2 cc. of the solution and mixing with 25 cc. sodium carbonate; the blue color is compared with the standard solution.

Reference: J. Biol. Chem. 12, 245 (1912).

# **FOLIN-DENIS REAGENT AND TEST FOR URIC ACID**

The addition of 2 cc. of reagent and 5-10 cc. saturated sodium carbonate solution to 2 cc. uric acid solution produces a blue color.



Reagent: 10 gm. sodium tungstate are heated with 80 cc. 85% phosphoric acid and 750 cc. water for two hours, under reflux, cooled and diluted to 1 liter with water.

Reference: J. Biol. Chem. 12, 239 (1912); 13, 263 (1912); 20, 619 (1915); 38, 83 (1919); 68, 123 (1926). Bull. Soc. Chim. Rom. 7, 65 (1926).

#### FOLIN-LOONEY DETERMINATION OF CYSTINE

1-5 gm. of dry protein are hydrolyzed with 25 cc. 20% sulfuric acid for 12 hours, in a kjeldahl flask, and diluted to 100 cc. 1-10 cc. of filtrate are treated with 20 cc. saturated sodium carbonate solution and 10 cc. of 20% sodium sulfite solution. 3 cc. of Folin-Denis' uric acid reagent are added, after 5 minutes, and the solution compared colorimetrically with a standard solution.

Reference: J. Biol. Chem. 51, 421 (1922).

#### FOLIN-LOONEY TRYPTOPHANE DETERMINATION

Tryptophane may be determined colorimetrically, in the same manner as tyrosine by the use of the Folin-Denis reagent. The blue color is compared with a standard. Reference: J. Biol. Chem. 51, 421 (1922); 69, 519 (1926).

#### FOLIN-McELLROY TEST FOR GLUCOSE

Reagents—(1) 200 gm. of crystalline sodium phosphate and 50 gm. sodium thiocyanate are triturated in a porcelaine mortar and, after 10 minutes, mixed with 100 gm. anhydrous sodium carbonate. (2) A 5.9% solution of copper sulfate. 0.4-0.5 gm. of (1) are added to 5 cc. of (2), heated until dissolved

and about 1 cc. urine added.

Reference: J. Biol. Chem. 33, 513 (1918); 38, 287 (1919).

#### FOLIN REAGENTS FOR CREATININE

I. Creatinine, with picric acid, forms a difficultly soluble picrate.

II. Based on the Jaffé test, creatinine is determined colorimetrically with the following solutions: (1) 1.2% aqueous picric acid; (2) 10% sodium hydroxide solution; (3) 0.5N potassium dichromate solution for comparison.

Reference: Zeit. physiol. Chem. 41, 235. Biochem. J. 7, 445 (1913).

#### FOLIN'S REAGENT

A test reagent for amino acids.  $\beta$ -naphthoquinone sulfonic acid in the presence of strong alkalis gives a deep red color in the presence of most amino acids. It is used as a method for colorimetric estimation of an amino acid.

#### FOLIN TEST FOR EPINEPHRINE (ADRENALINE)

Epinephrine may be detected, even at dilutions as high as 1:3000000, by the blue color produced on treatment with phosphotungstic acid solution.

Reference: Med. Klin. 1913, 266. J. Biol. Chem. 13, 477 (1913).

#### FOLLICLE

A small sac.

#### FOLLICLES, HAIR See Hair.

#### FOLLICLE STIMULATING HORMONE

F.S.H., one of the hormones produced by the hypophysis. It causes an increase in the number of follicles in the female, and spermatogenesis in the male. It causes a flow of estrogens, but not androgens. The structure is apparently

that of a protein. Old name, Prolan A.

**FOLLICULAR CELLS**

The enveloping cells serving as a bag for an ovum.

**FOLLICULIN**

See Estrone.

**FOLLICULIN HYDRATE**

Estriol.

**FOLLICULIN TEST**

See Koscis-Bughi.

**FOODS**

See Digestion.

**FOOD VACUOLES**

See Digestion.

**FORAMEN**

A perforation, as in a bone or membrane or shell.

**FOREBRAIN**

Central hemispheres of the brain.

**FOREMAN'S TITRATION**

A method of determining the carboxyl group in amino acid mixtures, based on the fact that amino groups do not react basic in 85% ethyl alcohol, thus allowing direct titration of the acidic group.

**FOREST PATHOLOGY**

See Agricultural Biochemistry.

**FORMALDEHYDE THEORY (OF PHOTOSYNTHESIS)**

A theory for the photosynthetic formation of carbohydrates in plants; which states that formaldehyde is the first product of photosynthesis and is condensed into the sugars. There are various mechanisms put forward to explain these reactions, but none have been proven.

**FORMIC ACID THEORY (OF PHOTOSYNTHESIS)**

A theory of photosynthetic carbohydrate formation in plants which states that carbon dioxide unites

with water to form formic acid, which is then polymerized to carbohydrates.

**FORMIC DEHYDROGENASE (BACT. COLI)**

A cytochrome-reducing dehydrogenase which catalyzes the oxidation of formic acid to  $\text{CO}_2$ , no external coenzyme being necessary.

**FORMIC ENZYME**

The pyridinoprotein enzyme which catalyzes the oxidation of formate to carbon dioxide and water in presence of coenzyme I.

**FORMOL TITRATION**

A method of estimating carboxyl groups in amino acids and in proteins by binding amine groups with formaldehyde (not applicable to guanidine nucleus and hence to arginine).

See also Autolysis.

**FORSSMAN ANTIGENS**

See Antigens (heterophile).

**FOUCHET TEST FOR BILE PIGMENTS IN BLOOD, FECES AND URINE**

10 cc. of urine and 5 cc. of 10% barium chloride solution are mixed and centrifuged. A small amount of a solution of 5 gm. trichloroacetic acid and 2 cc. 10% ferric chloride solution in 20 cc. water is poured over the precipitate; a green color is developed in a few minutes. For blood, 5 cc. of clear serum are treated with 5 drops of reagent.

Reference. Compt. rend. soc. biol. 80, 826 (1917). Münch. med. Wochschr. 1917, 1217.

**FOVEOLATE**

Pitted.

**FRAMBESIA**

See Yaws.

**FRANGULIC ACID**

See Emodin.

**FRANKE TEST FOR BILIRUBIN IN URINE**

Shake 5 cc. urine with 1-2 drops 0.2% methylene blue solution; a green color, sensitive to 1:500000, is produced.

Reference: Med. Klin. 27, 94 (1931).

**FRAXIN**

$C_{16}H_{18}O_{10}$ ; a glycoside of the bark of the ash, consisting of glucose and fraxetin; it crystallizes as needles from alcohol, m.p. 320°.

**FREDHOLM REACTION FOR POTASSIUM**

Potassium may be detected and determined by the well defined, crystalline, sparingly soluble precipitate produced by interaction of the ion with dilituric acid (5-nitrobarbituric acid).

Reference: Zeit. anal. Chem. 104, 400 (1936).

**FREE-MARTIN**

An external female animal with masculine internal development.

**FREHDEN-GOLDSCHMIDT TEST FOR PROTEIN**

A small amount of sample is moistened with a saturated glacial acetic acid solution of p-dimethylaminobenzaldehyde and treated with 1 drop of concentrated hydrochloric acid, producing a violet coloration.

Reference: Mikrochim. Acta 1, 338 (1937).

**FROGS' SPAWN**

Concretions of a cartilaginous character formed in mucus fermentations, also known as "la fermentation visqueuse."

**FRUCTOSE**

Levulose; fruit sugar; only hydrolytic product of inulin. Like

glucose shows various ring forms and optical isomers in solution, along with mutarotation. As part of the molecule of sucrose it is a prominent constituent of the diet. The Harden-Young ester is  $\alpha$ -fructose-1,6-diphosphoric acid and is involved in fermentation and carbohydrate metabolism, where it is in equilibrium with the Robison-Embsden ester which is glucose-6-monophosphoric acid.

See Glucose, Carbohydrate Metabolism.

**FRUCTOSEDIPHOSPHORIC ACID**

Alpha-fructose-1,6-diphosphoric acid; an important intermediate in the conversion of hexose to lactic acid; also formed in hydrolysis of sugar by yeast in the presence of phosphates. See Carbohydrate Metabolism.

**FRUCTOSURIA, ESSENTIAL**

See Glycosurias, Non-Diabetic.

**FRUITS, SEEDLESS**

See Plant Growth Hormones.

**F. S. H.**

Follicle Stimulating Hormone.

**FUCOSAN**

Polymer of l-fucose which forms cell walls of sea weed.

**d-FUCOSE**

A methyl pentose found in the glycosides, convolvulin and turpethin; rhodose (old name).

**l-FUCOSE**

A methyl pentose of sea weeds, m.p. 144°.

**FUCOSTEROL**

$C_{29}H_{48}O$ ; m.p. 124°, the sterol of sea weed.

**FUCOXANTHIN**

See Carotenoids.

**FUJITA-IWATAKE-MIYATA  
TEST FOR ASCORBIC ACID  
(VITAMIN C)**

A sky blue color is produced when 4 cc. of a solution of the substance in 2% metaphosphoric acid are treated with 1 cc. of a freshly prepared solution of 2 gm. sodium tungstate in 10 cc. N sulfuric acid, followed by the addition of 0.4 cc. 2N sodium hydroxide. 4.61 mg. ascorbic acid produces the same shade given by 1 mg. night blue. Reference: Biochem. Zeit. 277, 296 (1935).

**FULGERATION**

See Urology.

**FUMARATE-SUCCINATE  
SYSTEM**

See Succinic Acid Cycle.

**FUMARIC ACID**

Occurs in Iceland moss and is formed by various moulds; ethylenedicarboxylic acid, m.p. 300° C.

**FUMARIC ACID  
DEHYDROGENASE**

An enzyme from yeast catalyzing the reaction between fumaric acid and reduced dyestuffs, such as lactoflavin.

**FUMARINE**

See Protopine.

**FUNDUS**

Bottom of organ; posterior part of eyeball.

See Gastro-Enterology.

**FUNGI**

See also Cellulose Decomposition, Microbiology.

**FUNGI, LUMINOUS**

See Bioluminescence.

**FUNGUS**

Class of non-chlorophyll plants, including bacteria, yeasts, moulds, rusts, mushrooms, etc.; thallophytes.

**FURANOSE**

Referring to or having the furane ring structure.

**FURFURAL**

Furfuraldehyde; furfurol; b.p. 161.7°; occurs in many essential oils, fusel oil.

**FUSEL OIL**

A mixture of levorotatory amyl alcohol, isoamyl alcohol and some lower alcohols and their esters with the lower fatty esters formed in yeast fermentations.

**FUSTIN**

See Flavonol Glycosides.

**FUZZ**

See Hair.

## G

### GADOLEIC ACID

$C_{19}H_{37}COOH$ ; present as glycerides in cod-liver, sperm and herring oil.

### GALACTANS

Hexosans derived from galactose by the loss of water; found in gums, algae, pectins, mosses, etc.

### GALACTIN

An earlier name for prolactin.

### GALACTOLIPIDS

Cerebrosides.

### GALACTOSANS

Polysaccharides found in plant structures. On hydrolysis they yield galactose.

### d-GALACTOSE

Isomer of glucose, half of milk sugar molecule; m.p.  $168^{\circ}$  of alpha form.

### GALACTOSE REAGENT

See Van der Haar.

### $\beta$ -d-GALACTOSIDASE

Lactase.

### GALACTOSIDES

Cerebrosides.

### GALACTOSIS

Milk formation; lactosis.

### GALACTOSURIA

See Glycosurias, Non-Diabetic.

### GALANGIN

See Flavonol Glycosides.

### GALIOSIN

A glycoside of 1:2:4-trihydroxy-anthraquinone-3-carboxylic acid.

### GALL BLADDER, PHYSIOLOGIC CAPACITY

The number of hours of bile secretion the gall bladder can store and concentrate.

### GALLIC ACID

3,4,5,-trihydroxybenzoic acid, m.p.  $253^{\circ}$  C., found in tea gall nuts, etc., as a constituent of tannins. See Gastro-Enterology.

### GALLOTANNIC ACID

Tannic acid.

### GALLSTONES

Concretions usually mainly of cholesterol with small amounts of fats, phospholipids and metals, formed in the gall bladder due to an injury or the presence of a foreign body.

### GAMETE

A sex cell; conjugant; gonium; gonidium; gonoblast; nematogone; thelyblast.

### GAMIC

Pertaining to fertilization.

### GAMONES

Female sex determining factors, e.g. dimethyl esters of crocetin, a carotenoid dicarboxylic acid, effective for certain algae.

**GANGLIA**

See Nervous System.

**GANOIN**

Shiny enamel-like material of fish scales.

**GARROD TEST FOR HOMOGENITIC ACID**

The acid is converted to the lead salt, dissolved in ether and decomposed with hydrogen sulfide, leaving the free acid in the ether; evaporation of the solvent yields crystals melting at 146-147°. This is said to be the most reliable test for the acid.

Reference: J. Physiol. 1899, 512. Zeit. physiol. Chem. 78, 307 (1912).

**GAS EXCHANGE**

See Respiration.

**GAS GANGRENE**

See Toxicology.

**GASTRIC TESTS**

See Wagenaar.

**GASTRIN**

A substance or substances found in pyloric mucous membrane which on injection causes increased flow of gastric juice. According to some, gastrin is histamine, this substance causing a copious flow of the acid-secretion of the stomach. Pilocarpine also stimulates the flow of the enzymes and other organic materials.

**GASTRO-ENTEROLOGY**

Gastro-enterology is that branch of internal medicine which deals with the physiology, pathology and treatment of the organs of digestion. The organs concerned with the process of digestion begin with the mouth cavity and its associated salivary glands, continuing with the pharynx, the esophagus, stomach, small intestine, colon, down to the

rectum and anus. Supplementary digestive organs include the liver pancreas, and the organs comprising the bile tract.

The lips, teeth, cheeks, tongue, palate, pharynx and the salivary glands, the parotid, submaxillary and sublingual, are all concerned with the earliest steps of digestion. When these organs are diseased or missing proper mastication is interfered with and disturbance in digestion is prone to appear. The most important constituents of the saliva are a diastatic enzyme known as ptyalin, mucin, maltase, sulphocyanide of potassium, carbonate, and other inorganic ions.

One of the most important functions of the saliva is that of a solvent of various foodstuffs which facilitates the preparation of the food bolus as well as its swallowing. The diastatic ferment causes the starches to undergo their preliminary digestion. Saliva is believed by some investigators to possess also a high antiseptic action.

**Esophagus**

The esophagus or gullet is the beginning of the true digestive tract. It is a muscular membranous canal about nine inches long extending from the pharynx to the stomach.

After the food is mixed with saliva and well lubricated it is pressed backward by the tongue and pushed through the pharynx. Fluids or soft foods pass rapidly down the esophagus in a second or less, while it takes about four seconds for the passage of solid or thick foods.

Stenosis or obstruction of the esophagus is a common pathological finding in diseases of the esophagus.



It may be functional, due to hysteria or neurosis and is relieved in mild cases by sedatives. In more obstinate cases it is relieved by dilatation with instruments, or it may be organic due to changes in the esophageal wall.

Some of the pathological conditions responsible for organic changes are the malignancies, ulcerations either caused by the swallowing of caustic substances, tuberculosis or syphilis. Diverticuli (pouches), polypi (mucus membrane tumors attached to the wall of the organ by a stem) and varices (tortuous veins) are among the esophageal pathological conditions encountered.

Obstruction, complete or partial, and irregularities in the contour of the esophagus may be caused by pressure from external organs adjacent to the esophagus; such as an enlarged thyroid gland, heart and blood vessels, abscesses, etc.

The chief diagnostic means of abnormalities of the esophagus are fluoroscopic and roentgenographic examination with opaque mixtures, usually barium sulphate, and esophagoscopy (by use of an artificially lighted speculum inserted through the mouth into the esophagus).

The malignancies of the esophagus have at the present day a mortality of close to one hundred per cent.

The treatment is radium, deep roentgen-ray therapy, and in some early cases, surgical resection.

### The Stomach

The stomach is a hollow muscular organ with a secreting surface. It consists of three layers; an outer

or serous layer, an inner or muscular layer with circular and longitudinal fibers, and the third, the mucosa with its secretory glands. The stomach serves as a reservoir for the food ingested. It completes the mechanical subdivision of the food and prepares it for the small intestine. It starts the digestion of proteids and carries it to the acid albumin and proteose stage.

The stomach based upon its physiological activities divided into: cardia (upper part of stomach adjacent to the diaphragm), fundus (body of stomach), antrum (lower part of stomach adjacent to its opening), and pylorus (opening from the stomach to the small intestine).

Under fluoroscopy, shortly after ingestion of the barium meal, peristaltic waves begin at the fundus of the stomach passing down to the antrum. The antrum waves are deep constricting waves pushing the meal toward the pylorus. The pylorus opens only occasionally, not with every peristaltic wave. These waves churn up and macerate the food. The diastatic action of ptyalin on the starches begun in the mouth may continue for a time in the fundus of the stomach and is then checked by the presence of free acid.

The gastric secretion appears shortly after the ingestion of food. It contains not only pepsin but hydrochloric acid. The acidity is normally regulated by the regurgitation of small amounts of alkaline pancreatic secretion through the pylorus.

The stomach is examined by means of a barium meal. The routine time of examination is during the meal, six hours after-

ward, and twenty-four hours afterward. Both the fluoroscope and x-ray films are used; the two methods supplement each other. The interior of the stomach can now be examined by direct visualization by means of the gastroscope (a flexible tube, artificially lighted, containing several lenses).

Gastric analysis is another important aid in the diagnosis of gastro-intestinal diseases. The old standard test meal is the Ewald test-breakfast, consisting of one and one-half slices of stale bread, with one and one-half glasses of water. This is taken when the stomach is empty. The stomach contents are withdrawn at the end of one hour by means of a tube passed into the stomach. The examination of the test-breakfast residue consists in testing the secretion, the quantity, presence of mucus, or blood, amount of free hydrochloric acid and total acidity.

In order to distinguish true achylia (absence of free hydrochloric acid) from false, the histamine test is used. This is done by the injection under the skin of 0.2 to 0.3 cc. of 1/1000 histamine solution (imido-Roche).

Peptic or stomach ulcer and cancer of the stomach are of chief concern to the gastroenterologist. The cause of peptic ulcer is still debatable. Its size varies from  $\frac{1}{2}$  inch to 2 inches. It may be funnel-like and deep, or more extensive and shallow. Peptic ulcers may heal spontaneously; burrow into a blood vessel and induce a hemorrhage; perforate through all the layers of the stomach wall and produce peritonitis; or cause an obstruction to the passage of food through the stomach by forming a scar at its

opening in the process of healing.

Peptic ulcers are treated either medically or surgically.

Cancer of the stomach should be diagnosed at the earliest possible moment followed by prompt surgical removal of the malignant tissue. Cancer of the stomach is responsible for more than half of the total cancer mortality in most countries.

### The Small Intestine

The small intestine is arranged anatomically into the first portion of the duodenum, which is fixed, and a movable second and third portion. The first portion surrounds the head of the pancreas. Under X-ray it appears as a smooth pointed globular cap. The second portion of the duodenum contains the openings of the bile and pancreatic ducts. The jejunum and ileum comprise the rest of the small bowel. The small intestine has four layers: an inner mucosal, a submucosal, a muscular, and a serosal layer. The mucosa contain the villi, the glands of Lieberkuhn, lymphatic tissue and large lymph nodes.

In the small intestine the main portion of the digestion of the food is carried on. The starches and sugars are broken down into simple monosaccharides and absorbed as such. The fats are split into fatty acids, glycerin and soaps. The final digestion of proteins takes place through the proteose, peptone and polypeptide stage, down to their breaking up into the amino acids.

The two common lesions seen in the small intestine are duodenal ulcer and obstruction. Lesions of the jejunum and ileum are not very common and clinical diagnosis is difficult.

The two methods of examination of the small intestine are by plain films of the abdomen in the presence of gas and after a barium meal. The progress of the barium meal is watched by repeated fluoroscopic and film examinations during the first six-hour period in order to detect obstruction or deformity.

### The Large Intestine

The large intestine is about 5 feet in length. It has four layers; an inner mucosa, somewhat similar to the small bowel; a submucous layer; a muscular coat with internal circular and external longitudinal muscle layers and finally a serous coat. The cecum is the first part of the large bowel into which the small intestine is inserted by means of the ileocecal valve and from which the vermiform appendix arises. The rest of the colon is divided arbitrarily into the ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon and sigmoid.

The colon plays little part in the digestion and absorption of food stuff. It is mainly concerned with water absorption, cellulose digestion and excretion.

Peristalsis is slow and intermittent in the large bowel. There is mass movement of the contents of the distal half of the colon once or twice a day. Spinal reflexes control the terminal end of the bowel, so that filling the rectum results in a reflex which causes contraction and evacuation of the bowel.

In examination of the colon, both barium meal and barium enema are used, the latter is the more important.

The outline of the colon may be

changed by the filling defects of tumors or adhesions, or by kinking. The length and size of the colon may be abnormal. Spastic narrowing occurs in some cases of constipation and colitis, and organic narrowing in cancer and tuberculosis. In diarrheas the contents of the colon are seen, fluoroscopically, to rush through and in constipation the progress is slow.

The rectum filled with barium is smooth. Cancer, ulcerations, syphilis, tuberculosis or lymph granulomas produce irregular defects. All lesions in the rectum are better diagnosed by direct vision through the proctoscope (an artificially lighted tube inserted into the rectum).

The sigmoid, the part of the colon beyond the rectum, can be observed by a longer tube, about 12 inches in length, called the sigmoidoscope.

The common lesions of the colon are cancer, ulcerative colitis, tuberculosis and diverticulitis.

Cancer of the colon if diagnosed early and resected will prolong life for many years.

Ulcerative colitis, producing ulcerations in the colon, of unknown cause, is a chronic illness.

Tuberculosis of the intestine is generally secondary to pulmonary tuberculosis elsewhere.

Diverticulitis are inflamed small pouches or pockets protruding from the wall of the intestine which may become either abscessed or perforate into the peritoneal cavity.

Acute appendicitis still has a large mortality because of late treatment in the early stages. Its cause is unknown. Death from

appendicitis is usually the result of peritonitis.

The infectious diarrheas are caused by various bacteria. The commonest are the amebic dysentery, acute bacillary dysentery due to the Flexner, Shiga, or Sonne organisms.

The diagnosis can be made in acute attacks by direct stool cultures or by the bacteriologic examination of the feces. Agglutination tests with the patients serum may be used in chronic cases.

### The Liver

The liver, one the largest organs of the body, is more concerned with the metabolism of the body than any other organ. Bile formation and bile secretion is one of its multiple activities.

One of the main functions of bile is to assist in the digestion as well as absorption of fats. Bile checks the activity of pepsin but enhances the digestive power of the pancreatic juice. Bile salts have a mild stimulating influence on peristalsis.

Some of the diseases of the liver are: catarrhal jaundice, a mild inflammatory condition of the bile passages; acute yellow atrophy of the liver, a widespread destruction of the parenchyma of the liver; and various types of cirrhoses of the liver.

### The Gall Bladder

The gall bladder is a pear shaped organ about 8 cm. in length and contains about 50 cc. of bile. It is attached to the liver. It serves as a reservoir for the storage and disposal of bile after it is formed in the liver. The gall bladder has two important functions. It stores bile during fasting and it empties

this stored bile into the duodenum during digestion, especially of the fats in the food.

The gall bladder is a favorite seat for biliary calculi, mostly in persons beyond forty years of age. The theories for the causation of gall bladder disease are many. Severe inflammation of the gall bladder with suppuration, necrosis and perforation of the gall bladder wall and peritonitis may result.

X-ray is the method of choice in the diagnosis of biliary calculi. This depends on the administration of a special dye orally or intravenously, which when secreted in the bile reaches the gall bladder leaving a shadow on the X-ray film. In the presence of gall stones negative shadows will be observed. Pure cholesterol stones are not always visualized.

Biliary drainage for bile crystals will aid in the diagnosis of gall bladder calculi or cholelithiasis. The treatment in most cases is the total removal of the gall bladder.

### The Pancreas

The pancreas is a fairly large gland resembling the salivary glands in its structure. It consists of head, neck, body and tail and rests on the posterior wall of the abdomen. Its anterior surface is covered by the posterior wall of the stomach.

The pancreatic duct extending through the substance of the gland passes obliquely through the wall of the duodenum terminating in an orifice common to it and the common bile duct.

The pancreatic juice digests all types of foods. It contains three

important ferments: amylase which splits up the starches; lipase which splits up fats; and trypsin which digests the proteids. Chemically it contains sodium chloride, sulphate, phosphate, as well as calcium, magnesium and sulphur. The enzymes of the pancreas are activated by the intestinal juices and enhanced by the bile salts.

Some of the diseases of the pancreas are acute hemorrhagic pancreatitis which comes suddenly, death often resulting in several hours; acute pancreatitis, an acute infection of the pancreas occurring during the course of the disease of the stomach and duodenum; and chronic pancreatitis. This condition may follow acute pancreatitis. Calculi of the pancreatic duct, cysts and malignancy also may involve the pancreas. Diagnosis of diseases of the pancreas is extremely difficult and is generally made at operation.

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#### REFERENCES

- Alvarez: An Introduction to Gastro-enterology. Hoeber.  
Eusterman Balfour: The Stomach and Duodenum. Saunders.  
Kohn: Disease of the Digestive Tract. Davis Co.  
Rehfuß: Medical Treatment of Gall Bladder Disease. Saunders.  
White: Diseases of Digestive Tract. Nelson Medicine.

#### GASTROINTESTINAL DRUGS

See Pharmacology.

#### GASTROPODA

See Mollusca.

#### GASTROSCOPE

See Gastro-Enterology.

#### GASTRULA

Stage of embryonic development,

formed from the blastula by invagination of cells in the vegetative hemisphere and downward migration of cells of the animal hemisphere.

#### GAULTHERIN

$C_{14}H_{18}O_8.H_2O$ ; a glycoside of Gaultheria procumbens used in rheumatism, consisting of glucose and methylsalicylate; it crystallizes as needles or prisms from alcohol, decomposing at  $200^{\circ}C$ .

See Primeverose.

#### GELATIN

A protein derivative made by treating collagens with superheated steam, or boiling in dilute acids. One of the distinguishing characteristics of gelatin is its ability to make heat-reversible gels. Often classified as an albuminoid.

#### GELSEMIUM

Dried roots and rhizome of Gelsemium sempervirens containing the alkaloids gelsemine and gelseminine which are respiratory poisons; used as soporific.

#### GENE

One of paired, localized particles constituting the chromosomes which act as carriers of hereditary characters.

#### GENE, BIOCHEMICAL ASPECTS OF THE

See Genetics, Biochemical.

#### GENETICS

Study of heredity and evolution by variations.

#### GENETICS, BIOCHEMICAL ASPECTS OF

As contrasted with "classical genetics," which is concerned with the mechanism by which hereditary characters are transmitted from one generation to another, biochemical



genetics has to do primarily with the general question of how genes, the hereditary determiners, produce their characteristic effects. It may be said to differ from physiological and developmental genetics in that it attacks the general problem of gene action at the level of the biochemical reaction rather than at the higher levels of functional and structural organization.

The existence of genes was first inferred from the data of classical genetics. The rules by which they are transmitted indicate that they are particulate and are carried in groups (chromosomes) within which definite sequential relations obtain. The relation of the genetically inferred genes to the observed chromosomes was made possible by the techniques of cytology.

By means of biochemical methods the properties and modes of action of genes can be studied in either of two principal ways, viz., (1) by investigating the chemical properties of chromosomes and genes themselves, or (2) by inferring from biochemical descriptions of hereditary characters something as to the properties of the antecedent genes.

Direct chemical analyses of chromatin from sperms indicate that chromosomes are composed mainly of thymonucleic acid (ca. 60%) combined with histones and protamines (together ca. 35%). Staining methods and the ultraviolet absorption method of Caspersson indicate that the nucleic acid is concentrated in the dark-staining bands of the giant salivary gland chromosomes of *Diptera*. Enzyme digestion experiments by Caspersson and by Mazia show that nuclease breaks down this nucleic acid component but does not destroy the continuity

of the chromosome. Trypsin, on the other hand, does destroy the basic structure, a fact consistent with the assumption that the continuity depends on histones and protamines. As expected on this assumption, pepsin does not destroy chromosome continuity.

As described by Stanley and others, viruses show several striking similarities to genes, among them, rough similarity in size, reproduction in living cells, presence of nucleic acid, mutability, and production of specific phenotypic effects. If an essential similarity between viruses (including phages) and genes can be firmly established, much that is learned of one can be carried over to the other. (See discussions by Muller).

Hereditary characters in many organisms have been at least partly described in terms of their component biochemical reactions. The hereditary abnormality alcaptonuria in man, for example, is characterized by an inability to oxidize homogentisic acid (Garrod). As a consequence, this metabolic derivative of phenylalanine and tyrosine is excreted in the urine. A somewhat similar situation is found in phenylketonurics. Here there is an inherited inability to oxidize phenyl pyruvic acid to p-hydroxyphenyl pyruvic acid. A significant and interesting aspect of this disease is the fact that it is invariably associated with imbecility or idiocy (Fölling, Penrose). The usefulness of such gene-controlled disturbances as these in interpreting normal metabolism has been pointed out by Haldane and others but nevertheless has been only inadequately appreciated by biochemists, physiologists, and others.



Flower pigmentation has been studied extensively both genetically and biochemically. The substances concerned are mainly anthocyanins, anthoxanthins, carotenoids, and so-called co-pigments (see review by Lawrence and Price). The presence of these pigment components is dependent on gene activity, and they may be genetically modified either quantitatively or qualitatively. Among the qualitative variations in anthocyanins, state of oxidation, glycosidal type, and degree of methylation are determined by genetic constitution. Anthocyanins are pH indicators, and genes are known which influence pigmentation by determining the pH of cell sap. In the dahlia correlations in amounts of different pigment components have been found which indicate that the normal biosyntheses of anthocyanins, flavones, and chalcones involve a common precursor. If more of one component is produced, this tends to be at the expense of the other two.

Wright and others have made extensive genetic studies of melanin pigmentation in mammals. For the guinea pig, Wright has drawn up an ingenious detailed scheme of gene action based largely on genetic data. This scheme postulates that genes act by exerting more or less direct control over reaction rates. Because of the difficulty of working with melanin pigments chemically, unfortunately many of the biochemical predictions of the hypothesis cannot be readily tested.

By methods somewhat similar to those used by Wright in his interpretation of pigment interactions in the guinea pig, studies have been made of the development of eye-pigment components in *Ephesia*,

*Drosophila*, and other insects. A number of biochemical predictions made from the data of genetic and transplantation experiments have been verified. Thus tryptophane and kynurenine have been identified as precursors of the brown pigment component.

Kimball finds that mating types in *Euplotes* are genetically controlled and that the control involves the production of specific substances. There are six mating types dependent on three alleles of a single gene. The six types are accounted for by the three homozygotes plus the three heterozygotes. Apparently the mating types are characterized by three specific substances, produced singly by the three homozygotes and in combinations of two by the heterozygotes. The suggested one-to-one relation between gene and substance in this situation is reminiscent of the direct relation generally found between gene and antigen in genetically determined immunological characters. Irwin and Cole and co-workers, for example, find that in general in the pigeon and dove hybrids with which they have worked, there exist simple relations between genes and agglutinogens. There are, however, so-called "hybrid substances" produced in certain combinations which appear to depend on interactions of genes from the two parents.

Winge and Laustsen find that the abilities of yeasts to utilize certain disaccharides vary with different strains. In the hybrids investigated the ability to decompose a given disaccharide, presumably contingent on the presence of a specific enzyme, is dominant to the alternative inability.

On the assumption that biochemi-

cal reactions in general are controlled by genes, Beadle and Tatum have tested X-ray-treated material of the red bread mold *Neurospora* for loss of ability to synthesize specific growth factors. In this way a mutant strain has been found which is unable to grow in the absence of p-aminobenzoic acid. Another requires the thiazole half of the thiamin molecule and a third is unable to grow in the absence of pyridoxin. In each case the inability to carry on the synthesis results from a modification of a single gene.

From facts such as those reviewed here, it seems likely that genes are specific protein molecules or groups of molecules possessing the power of reproduction under appropriate conditions in living cells. As a working hypothesis it may be supposed that their primary function is that of controlling protein specificities either by serving as models or in some other way. Since on this assumption enzyme specificities are referable to gene specificities, genes may be thought of either as synonymous with enzymes or as bearing a one-to-one relation to them. While experimental data dealing directly with this point are not abundant, there are suggestions that each enzymatically catalyzed reaction is under the direct control of one particular gene and, conversely, that each gene controls in a primary way one specific reaction. While it is probable that these considerations are based on concepts that are too simple, they may nevertheless serve to indicate that any complete view must regard genes as integral parts of the biochemical system rather than as hypothetical units conceived merely to be juggled by geneticists in the solution

of intricate puzzles of heredity.

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## REFERENCES

- Beadle, G. W.: *Ann. Rev. Physiol.*, 1: 41, 1939.  
Beadle, G. W. and E. L. Tatum: *Proc. Natl. Acad. Sci.*, 27: 499, 1941.  
Darlington, D. C.: *Recent Advances in Cytology*, Ed. 2. Churchill, London, 1937.  
Garrod, A. E.: *Inborn Errors of Metabolism*, Ed. 2. Oxford Med. Pub., 1923.  
Goldschmidt, R.: *Physiological Genetics*. McGraw-Hill, New York, 1938.  
Gulick, A.: *Quart. Rev. Biol.*, 13: 1 and 140, 1938.  
Haldane, J. B. S.: *New Paths in Genetics*, Harper & Bros., New York, 1942.  
Kimball, R. F.: *Genetics*, 27: 269, 1942.  
Lawrence, W. J. C. and J. R. Price: *Biol. Rev.*, 15: 35, 1940.  
Muller, H. J.: *Cold Spring Harbor Symposium on Quant. Biol.*, 9: 290, 1941.  
Stanley, W. M.: *Physiol. Rev.*, 19: 524, 1939.  
Strandskov, H. H.: *Ann. Rev. Physiol.*, 4: 49, 1942.  
Sturtevant, A. H.: *Ann. Rev. Physiol.*, 3: 41, 1941.  
Winge, O. and O. Laustsen: *Compt. rend. Lab. Carlsberg, Serie physiol.*, 22: 337, 1939.  
Wright, S.: *Physiol. Rev.*, 21: 487, 1941.

## GENETICS, CLASSICAL

See Genetics, Biochemical.

## GENETYPE

Genotype; genoplast; a group of genetically similar individuals.

## GENINS

See Aglycones.

## GENITO-URINARY TRACT

See Urology.

## GENOBLAST

Sex cell.

## GENOMORPHINE

Morphine-N-oxide, m.p. 274-5°, less toxic than morphine, non-habit forming.

**GENOSCOPOLAMINE**

Scopolamine-N-oxide, m.p. 80°, said to be less toxic and more potent than scopolamine.

**GENOTYPE**

See Genotype.

**GENTIAN**

Dried root of *Gentiana lutea*; extracts used as bitters.

**GENTIANASE**

See Enzymes, Non-Proteolytic.

**GENTIANOSE**

$C_{18}H_{32}O_{16}$ ; a non-reducing trisaccharide,  $\alpha$ -gentiobiosyl D-fructofuranoside or,  $\beta$ -D-glucopyranosylsucrose, which occurs in the rhizomes of the gentian species from which it is extracted with alcohol; on hydrolysis with invertase it gives fructose and gentiobiose; m.p. 209°.

**GENTICAULIN**

See Primeverose.

**GENTIOBIASE**

See Enzymes, Non-Proteolytic.

**GENTIOBIOSE**

A reducing disaccharide found in many glycosides, usually prepared from the trisaccharide gentianose. It is glucopyranose-6- $\beta$ -glucopyranoside.

See Disaccharides.

**GENTISIN**

A trihydroxyxanthone pigment, obtained from the gentian root.

**GENUS**

A group of related species.

**GEOTROPISM**

Reaction to gravity.

**GERANIOL**

A terpene alcohol of frequent occurrence; rose odor, m.p. 82°, b.p. 230°.

**GERANTOTHERAPY**

(BENJAMIN)

The treatment of the ageing

process as an entity, or of senescence and senility as such. It is distinguished from geriatrics which limits itself to diseases of old age.

**GERATOLOGY**

Study of old age.

**GERIATRICS**

See Gerantotherapy.

**GERM**

A cell or part of organism capable of development into an offspring.

**GERM CELL**

Sex-cell; gamete; unfertilized ovum or spermatozoon.

**GERMINAL DISC**

Active protoplasm in yolk of segmenting egg which originates the embryo.

**GERMINAL EPITHELIUM**

Cell layer of early mammalian ovary which forms ova and follicles.

**GERM PLASM**

Nucleus of gamete; idioplasm.

**GERONTINE**

See Spermine.

**GERONTOLOGY**

Science of old age.

**GERRARD TEST FOR**

**ATROPINE AND**

**HYOSCYAMINE BASES**

An alcoholic solution of the base is heated with an aqueous or alcoholic solution of mercuric chloride, forming a brick-red precipitate of mercuric oxide along with the alkaloid hydrochloride. Daturine and duboisine, but not scopolamine, also give this reaction.

Reference: Zeit. anal. Chem. 24, 601 (1885). Pharm. Ztg. 1884, 683.

**GESTATION**

Period between fertilization and parturition, (in days: mouse 21, hare 28, dog 60, pig 119, sheep 150, man 280, horse 325, elephant 850.)

# GIEMSA TEST FOR QUININE

A solution of 10 gm. potassium iodide in 50 cc. water is mixed with a solution of 27 gm. mercuric chloride in 1500 cc. water and 2 cc. of glacial acetic acid added; an opalescence at dilutions as high as 1:100000 to 400000, is obtained with quinine solutions.

Reference: Arch. Schiffs-u. Tropen-Hyg. 12, 78 (1908). Biochem. Zeit. 9, 207 (1929).

# GINGER

Dried rhizome of *Zingiber officinale*, contains "gingerol"; carminative and flavor.

# GINGIVA

See Teeth, Biochemistry of.

# GIRARD'S REAGENT

A name originally applied to one compound, trimethylamino aceto-hydrazide hydrochloride, but since grown to include several compounds, which form water-soluble ketone derivatives, and so serve as a means of purifying them.

# GITALIN

See Digitalis Glycosides.

# GITOGENIN

See Digitalis Glycosides.

# GITONIN

See Digitalis Glycosides.

# GITOXIGENIN

See Digitalis Glycosides.

# GITOXIN

See Digitalis Glycosides.

# GLAND

A cell organ which secretes and excretes physiologically active substances.

# GLANDS OF LIEBERKUHN

See Gastro-Enterology.

# GLASS ELECTRODE

An electrode used for determining hydrogen ion concentration, which is rapidly replacing all others. It is rapid, accurate, and does not in

any way contaminate the solution to be analyzed. It consists of the following concentration cell, with a glass membrane at the heavy line:

$\text{Hg}|\text{HgCl}, \text{KCl}|\text{Soln. I}|\text{Soln. II}|\text{KCl}, \text{HgCl}|\text{Hg}$  where solution I and solution II differ from each other in hydrogen ion concentration.

# GLAUCOMA

A disease of the eye in which the increased intraocular tension injures the eyeball, culminating in its hardening, opaque cornea, and cataract. The intraocular tension may reach 80 mm. of mercury and higher by tonometer. The disease may be acute or chronic and is difficult to control without surgery. Miotics, like physostigmine and pilocarpine salts, are employed widely.

See also Eye, Biochemistry of.

# GLAUGINE

An alkaloid,  $\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}$ , from herb *Glaucium luteum*, which paralyzes the heart, suspends the sensibility and influences the striated muscle while suspending the excitability.

# GLEET

See Gonorrhea.

# GLIADIN

The prolamine present in wheat and rye; a constituent of gluten.

# GLIADINS

In the American Classification of Proteins, the gliadins are simple proteins, soluble in 70-80% alcohol, but insoluble in water, absolute alcohol and other neutral solvents. Examples: gliadin from wheat, zein from maize.

# GLOBIN

Portion of a hemoglobin which is

combined with haem, a histone.

## GLOBULAR PROTEIN

### HYPOTHESIS

A theory relating to the nature of protein structure advanced by Svedberg. He finds that many proteins are globular in form. Long polypeptide chains may roll themselves up into this shape. He finds that particle weight of the proteins are multiples of 35,000.

## GLOBULINS

In the American Classification of Proteins, the globulins are simple proteins, insoluble in water, but soluble in dilute neutral solutions of salts of strong acids and strong bases. Example: serum globulin, and edestin of hemp seed.

## GLOBULIN X

An intracellular globulin found in muscle to the extent of about 20-25% of the total protein; insoluble in  $H_2O$ , soluble in oil, salt solutions, i.p. 5.2.

## GLOMERULONEPHRITIS

See Bright's Disease.

## GLOSSITIS

Sore tongue, one of the signs of pellagra, anemia and sprue.

## GLUCOCHEIROLIN

A Cheiranthus glucoside.

## GLUCONAPIN

A mustard glycoside.

## GLUCONEOGENESIS

The formation of glucose and glycogen (e.g. by the liver) from certain non-glucose substances.

## GLUCONIC ACID

$HOOC(CHOH)_4CH_2OH$ ; an oxidation product of glucose.

## GLUCOPROTEIN

See Glycoprotein.

## GLUCOSAMINE

2-amino-glucose, obtained from chitin (crustacean shells).

## GLUCOSAMINE—

### DIGALACTOSE

A carbohydrate complex frequently found in the protein molecule.

## GLUCOSAMINE—

### DIMANNOSE

A carbohydrate complex frequently found in the protein molecule.

## GLUCOSANS

(1) Hexosans derived from glucose by the loss of water. Examples: cellulose, starch, glycogen, etc.

(2) 1-6 anhydrides of two glucose molecules; alpha glucosan being prepared from alpha-glucose and beta-glucosan from beta-glucose.

## GLUCOSE

$C_6H_{12}O_6$ ; dextrose; corn sugar; grape sugar; starch sugar; forms a monohydrate and exists in numerous isomeric forms at least in solution allowing for its great variety of actions. A straight chain formula shows a free aldehyde group, oxide ring formulas make it potential but permit a space isomerism shown by  $\alpha$ - and  $\beta$ - forms of glucose. The forms  $\alpha$ -d-glucose and  $\beta$ -d-glucose are variants due to the pyranose ring. A furanose ring yields  $\gamma$ -glucose. The alpha form has a rotation of  $+110^\circ$ , the beta form  $+19^\circ$  and the gamma form  $+52.5^\circ$ . The various forms achieve equilibrium in solution, which accounts for a shift toward an equilibrium value of optical rotation, known as mutarotation. There are, however, possibly eight cyclic configurations in solution besides the straight chain, the pyranose (amylen oxide) ring predominating.

Glucose is involved in photosynthesis, fermentation, blood chemistry, muscle action, diabetes, dietary balance, etc., (which see).

**GLUCOSE ABSORPTION**

See Carbohydrate Metabolism.

**GLUCOSEEN**

Derivatives of an unsaturated anhydroglucose (Helferich).

**GLUCOSE ENZYME**

A pyridinoprotein enzyme of the liver which catalyzes the oxidation of glucose to gluconic acid, requiring coenzyme I.

**GLUCOSE METABOLISM**

See Creatine and Creatinine Metabolism.

**GLUCOSE OXIDASE**

**(ASPERGILLUS)**

An enzyme of the juice of *Aspergillus niger* which catalyzes the oxidation of d-glucose to gluconic acid, optimum pH 6, also attacks d-mannose and d-galactose.

**GLUCOSE TESTS**

See Agostini, Barfoed, Brown-Lum, Fehling, Folin-McEllroy, Herzfeld, Sumner Reagents.

**GLUCOSE TOLERANCE TEST**

See Carbohydrate Metabolism.

**GLUCURONIC ACID**

$\text{CHO} \cdot (\text{CHOH})_4 \cdot \text{COOH}$ ; an oxidation product of glucose; in the body it forms reaction products with many toxic agents, which are then excreted.

See Detoxication.

**GLUCURONIC ACID TEST**

See Jolles.

**L-GLUTAMIC ACID**

Alpha amino glutaric acid;  $\text{CO} \cdot \text{OH} \cdot \text{CH}(\text{NH}_2) \cdot (\text{CH}_2)_2 \cdot \text{COOH}$ ; rhombic tetrahedra, soluble in water, m.p. 197-8°; an acidic amino acid found in many proteins largely as the acid amide, glutamine.

**GLUTAMIC ACID**

**METABOLISM**

Glutamic acid may be oxidized to

$\text{NH}_3$  and alpha-ketoglutaric acid, which on  $\beta$ -oxidation ultimately yields  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . Alternately glutamic acid plus  $\text{NH}_3$  yields glutamine. It can form glucose, thus being anti-ketogenic.

**GLUTAMIC AMINOPHORASE**

A transamination enzyme of animal and plant tissues which promotes the conversion of glutamic and pyruvic acids to alpha-glutaric acid and alanine and vice versa.

**GLUTAMIC ENZYME**

(1) A pyridinoprotein enzyme which catalyzes the oxidation of l(+)-glutamic acid to alpha-ketoglutaric acid, in presence of coenzyme I; found in kidney, liver, heart; (2) a triosephosphopyridinoprotein enzyme which catalyzes the oxidation of l(+)-glutamic acid by coenzyme II.

**GLUTAMINASE**

An enzyme which promotes the mutual conversion of glutamic acid and glutamine, found in beet roots and blades of rye-grass.

**GLUTAMINE**

$\text{CO}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{COO} \cdot \text{H}$ ; the acid amide of glutamic acid, found in many proteins.

See Detoxication.

**GLUTATHIONE**

$\text{HOOC} \cdot \text{CH}(\text{NH}_2) \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CONH} \cdot \text{CH}(\text{CH}_2\text{SH}) \cdot \text{CONH} \cdot \text{CH}_2 \cdot \text{COOH}$ ; a tripeptide composed of cysteine, glycine, and glutamic acid. It occurs in plant and animal tissues both and may function as the intraorganismal transport of amino acids and biocatalytically through its sulfhydryl group is a participant in vitamin-reduction processes.

**GLUTATHIONE TESTS**

See Fischer-Fischl, Hopkins, Zimmet.



# GLUTELIN

Protein of wheat and gluten.

# GLUTELINS

In the American Classification of Proteins, are simple proteins, insoluble in all neutral solvents, but readily soluble in very dilute acids and alkalies. Some can be separated into two fractions by adding ammonium sulfate to an NaOH solution of the crude protein. At 3% saturation an alpha glutelin separates, at 16% saturation a beta glutelin separates. Example: glutenin from wheat.

# GLUTOSE

$\text{CH}_2\text{OH}(\text{CHOH})_2\text{CO}\cdot\text{CHOH}\cdot\text{CH}_2\text{OH}$ ; a hexose in which the keto group is on  $\text{C}_3$ ; it is not metabolized, nor is it effective in treating insulin shock.

# GLYCERIC ACID

Two forms of the monocarboxylic acid made from glycerine.

# GLYCERIC ACID TEST

See Egriwe.

# GLYCERIN TEST

See Hovey-Hodgins (in presence of glycol).

# GLYCEROL

$\text{CH}_2\text{OH}\cdot\text{CHOH}\cdot\text{CH}_2\text{OH}$ ; a syrupy, high boiling triatomic alcohol, which when esterified with fatty acids forms the fats, the latter being a source for glycerol. It is also prepared by yeast fermentation of carbohydrates.

# $\alpha$ -GLYCEROPHOSPHORIC ACID

A naturally occurring ester in the laevo form.

# $\alpha$ -GLYCEROPHOSPHORIC DEHYDROGENASE

A cytochrome-reducing dehydrogenase of practically every animal tissue which catalyzes the oxidation of 1(+)-alpha-glycerophos-

phate to glyceraldehydephosphate especially in presence of cytochrome c.

# $\alpha$ -GLYCEROPHOSPHORIC ENZYME

A pyridinoprotein enzyme of heart, intestine and skeletal muscle, which catalyzes the oxidation of alpha-glycerophosphate by coenzyme I, i.e. the d(-)-isomer only.

# GLYCINE

$\text{C}_2\text{H}_5\text{O}_2\text{N}$ , glycoll, amino-acetic acid; the simplest amino-acid; i.p. 6.09, large colorless prisms, m.p. 225-230°, sol.  $\text{H}_2\text{O}$ ; found in connective tissue, the keratins, and forms unabsorbable compounds with many poisons in the body.

# GLYCINE METABOLISM

In vivo, glycine undergoes several reactions: a) oxidation to  $\text{NH}_3$ ,  $\text{CO}_2$ , and  $\text{H}_2\text{O}$ , b) combination with benzoic acid analogues to form various hippuric acids, frequently for detoxification, c) combination with cholic acid to form glycocholic acid, d) formation of glucose in the diabetic. Glycine is anti-ketogenic. Under certain conditions, it is synthesized in the body.

See Amino-Acids, Physiology of.

# GLYCOCHOLIC ACID

$\text{C}_{23}\text{H}_{36}(\text{OH})_3\text{CONHCH}_2\text{COOH}$ ; the peptide combination of cholic acid and glycine; a form in which the bile acid is found in human and ox bile. See taurocholic acid.

# GLYCOCYAMIDINE

See Creatine and Creatinine Metabolism.

# GLYCOCYAMINE

Guanidine acetic acid, considered to be the physiologic precursor of creatine; converted to urea and glycine by glycocylaminase (of liver).

See Creatine and Creatinine Metabolism.

## GLYCOGEN

Animal starch; the characteristic fuel reserve carbohydrate of animals; it is a white, water dispersible powder, does not give a positive Fehlings test; hydrolyzes to glucose.

See Carbohydrate Metabolism.

## GLYCOGENASE

Any glycogen hydrolyzing enzyme found in animal tissues and in yeast.

## GLYCOGENESIS

The formation of glycogen of various types from sugars, amino acids and other suitable compounds.

See also Carbohydrate Metabolism.

## GLYCOGEN METABOLISM

See Creatine and Creatinine Metabolism.

## GLYCOGENOLYSIS

The conversion of glycogen into glucose; inhibited by insulin, caused by the enzyme glycogenase, and promoted by epinephrine.

See also Carbohydrate Metabolism.

## GLYCOGEN TEST

See Simon (in urine).

## GLYCOLIC ACID

Hydroxyacetic acid, m.p. 80°, a constituent of cane juice.

## GLYCOLIC ACID TEST

See Eegriwe.

## GLYCOLIPIDS

Compound lipids containing carbohydrates but no phosphorus, e.g. cerebrosides or galactolipids.

## GLYCOLLIC ACID

$\text{CH}_2\text{OHCOOH}$ , m.p. 80°, occurs in beet and sugar cane juice.

## GLYCOLYSIS

Breakdown of sugars in body.

## GLYCOLYTIC ENZYME COMPLEX

The heat-labile enzyme proper and the heat stable dialyzable coenzyme of fermentation found in cell-free muscle extract.

## GLYCOPROTEIN

In the American classification of proteins, a glycoprotein is a conjugated protein, where the non-protein group is a carbohydrate other than that of nucleic acid. Also called glucoprotein.

Examples: mucin of the snail; the proteins in the jelly of fish eggs.

## $\beta$ -GLYCOSIDASE

See Emulsin.

## GLYCOSIDES

A group of carbohydrate derivatives in which some organic group is attached to the oxygen of carbon of the sugar. Glycosides are frequently found in nature accompanied by their specific hydrolysis enzymes; often are extremely poisonous. The majority are crystalline, water and alcohol soluble solids.

## GLYCOSURIA

Mellituria; the appearance of glucose in the urine, may be due to food or "alimentary glycosuria" or "afternoon glycosuria"; in pathological conditions like diabetes, Addison's disease, pituitary disease, it is likely to be high and persistent.

## GLYCOSURIA, ALIMENTARY

See Glycosurias, Non-Diabetic.

## GLYCOSURIA, CEREBRAL

See Glycosurias, Non-Diabetic.

## GLYCOSURIA, EMOTIONAL

See Glycosurias, Non-Diabetic.

**GLYCOSURIA IN PREGNANCY**

See Glycosurias, Non-Diabetic.

**GLYCOSURIA, PHLORIZIN**

See Glycosurias, Non-Diabetic.

**GLYCOSURIA, RENAL**

See Carbohydrate Metabolism, Glycosurias, Non-Diabetic.

**GLYCOSURIAS, NON-DIABETIC**

The most commonly used test in this country for the detection of sugar in the urine is the Benedict test. The reagent consists of an alkaline copper solution and the detection of sugar depends upon the conversion of the soluble blue cupric oxide into an insoluble cuprous oxide under the influence of heat. Since it is a reduction test, it is necessary to know that urine may contain reducing substances other than glucose. They may be normal or abnormal constituents of the urine. The normal may be phosphates.

The abnormal constituents which may be found in the urine are glycuronic acid, lactose, galactose, pentose (xyloketose and arabinose) and fructose (levulose). According to Lasker and Enklewitz<sup>1</sup> while doing the Benedict test, it is possible to differentiate the reducing sugar by noting the amount of reduction after certain intervals and at the end.\*

\*Exton<sup>2</sup> by using a modification of Sumner's<sup>3</sup> di-nitro-salicylic acid method can also easily differentiate the various sugars.

Further differentiation can be carried out with the aid of the following tests\*:

1. Fermentation with baker's yeast  
Glucose and fructose are the only fermentable sugars.
2. By polariscopic examination  
Glucose will be found to be dex-

trorotatory and fructose levorotatory.

3. Selivanoff's test

Positive with fructose which can thus be differentiated from glucose.

4. Naphthoresorcinol test

Determines the presence or absence of glycuronic acid or glycuronates as the reducing substance.

5. Bial's test

Positive in pentosuria.

6. Mucic acid test

Positive only in the presence of lactose or galactose.

7. Lead Acetate test

Further identifies lactose.

8. For a more exact determination of the various sugars characteristic osazone crystals can be prepared by treating the urine with phenyl or methyl-phenylhydrazine. The crystals can further be distinguished by their melting point.

\*All the tests except No. 7 are described in Hawk and Bergeim.<sup>4</sup>

Reducing substances in the urine which are not due to glucose are usually found in small amounts from 0.1% to 0.6%. Glycuronates come and go. Pentose is a constant finding in essential pentosuria. Fructose varies in fructosuria with the diet. Lactose and galactose vary in the amounts. Glucose may be found in small and in large amounts.

The finding of glucose in the urine does not always mean diabetes mellitus. If the blood sugar is never found to be elevated, even in the glucose tolerance test, the glycosuria is called renal glycosuria. But even the finding of an elevated blood sugar does not always mean diabetes

since other conditions may cause hyperglycemia with glycosuria. The non-diabetic melliturias may thus be divided in two main groups, one without hyperglycemia and the other with hyperglycemia. The first group may show glucose or other reducing substances in the urine, while the second group shows only glucose.

### NON-DIABETIC GLYCOSURIAS WITHOUT HYPERGLYCEMIA

In the discussion of the non-diabetic glycosurias without hyperglycemia, one should mention a few words about the positive Benedict test in the presence of phosphates, glycuronic acid and glycuronates. Phosphates may give a slightly positive test with Benedict solution. It will be found after a high vegetable diet. The solution is not very opaque and the precipitate is coarse, flocculent and white or grayish. It is not a constant finding and it is related to meals. Glycuronic acid may appear in the urine as a compound or in free form due to spontaneous decomposition of the compound. It is usually found in the urine following the use of coal tar or other products (aspirin, salicylates, pyramidone, antipyrin, camphor, etc.). With the omission of the preparations, the Benedict test of the urine becomes negative. The naphthoresorcinol test gives a positive reaction.

The most important non-diabetic glycosuria without hyperglycemia is renal glycosuria. It is a glycosuria with a low renal threshold. It is called by some "renal diabetes" or "diabetes innocens". The urine contains glucose. It is fermentable and gives a negative Selivanoff reaction. In treating the urine with phenylhydrazine, typical glucosa-

zone crystals with a melting point of  $205^{\circ}$  are obtained. The blood sugar is within normal limits all the time. This means that the patient has a low renal threshold for sugar. There are no symptoms of diabetes. Renal glycosuria is inherited and therefore should be looked for in the relatives. Occasionally cases of true diabetes and renal glycosuria are observed in the same family. One of my patients has renal glycosuria for many years, while his brother has a severe diabetes with a low renal threshold, which complicates greatly the treatment of his diabetes. Some of the patients have a constant glycosuria, irrespective of the food, while others have glycosuria only off and on. Marble<sup>5</sup> calls as "typical" only those cases with renal glycosuria whose urine shows sugar all the time irrespective of the diet or fasting and in whom the blood sugar is never found above normal. All the cases with low renal thresholds, whose urine is sugar-free from time to time are considered by him as "atypical". True renal glycosuria is most likely a permanent condition from birth on. Whether in some the low renal threshold develops gradually due to the inherited tendency, there is no definite evidence as yet.

According to some authors patients with renal glycosuria may later develop true diabetes. Whether there is a transitory renal glycosuria there is not enough evidence except in pregnancy. The youngest case reported, that of a 20 month old infant,<sup>6</sup> showed a renal glycosuria only for six weeks and then the urine became sugar-free. One of my patients, a young man, showed renal glycosuria for the first time following the recovery from an acute mononucleosis. Allen, Wishart, and

Smith<sup>7</sup> reported a case in which severe trauma (shell concussion) in an adult led to renal glycosuria.

Most of my cases with renal glycosuria gave a positive family history. My youngest patient, a girl, was 2 year 8 months old (in 1931) when sugar was discovered in the urine, while the blood sugar was normal. For fear of overlooking a true diabetes, the child was treated, with the full consent of her mother, for about eight months with a diet and three daily doses of insulin. The amount of insulin varied from 6 units three times a day to 12 units in A.M. and 4 units in P.M. During that time she had some sugar-free urines and some insulin reactions. She had measles and other episodes with fever and acetonuria. Her venous blood sugar showed only a few abnormal tests. Her highest capillary test was 174 mg. per 100 c.c. of blood. After eight months of this treatment, the insulin was omitted and she resumed a normal diet. A glucose tolerance test gave a normal blood sugar curve. The girl is now 14 years old and in good health. She grew normally. Her urine still shows the same amount of sugar. My oldest patient is over 70 years. He was treated elsewhere for a mild diabetes with an eye complication. When his son was found by me to have a renal glycosuria, I suggested a check up on his father's diagnosis. He was brought for an examination and showed renal glycosuria.

Prolonged follow-up of patients with renal glycosuria by repeated glucose tolerance tests may show occasionally an elevated blood sugar in the curve. Caution should be taken to instruct the patient to follow a normal diet for at least a week preceding the glucose tolerance test

since the low carbohydrate diet may effect the test.

Phlorizin glycosuria is an experimental type of diabetes which was considered by some to be similar to renal diabetes because of the glycosuria in the presence of a normal blood sugar. It is produced by the subcutaneous injection of the glycoside phlorizin. Except that the blood contains less sugar, the metabolism is as seriously affected as in pancreatic diabetes. The damage is probably in the kidney, which causes the glycosuria, and also in the liver. There is an increased destruction of protein with sugar production (hyperglyconeogenesis). This fact distinguishes this from human renal diabetes.

Glycosuria in Pregnancy. Pregnancy is the only condition in which a true renal glycosuria is found to be transitory. It may recur in the same patient with each pregnancy. It is a frequent occurrence. It usually appears during the 30th and 33rd week and disappears just before and shortly after the birth of the baby or if the pregnancy is interrupted. Williams<sup>8</sup> found sugar in the urine four times as often in the second half. It has also been observed in animals. If in such animals the ovaries are removed, the glycosuria disappears, while the implantation of the ovaries of pregnant animals into non-pregnant will produce glycosuria<sup>9</sup>.

The presence of sugar in the urine of a pregnant woman should be taken seriously since occasionally it may be the onset of a true diabetes. Blood sugar studies as well as the determination of the type of sugar in the urine should be carried out and the condition should be followed for some time before a defi-

nite diagnosis is made. The presence of acetonuria is believed by some to make the diagnosis of diabetes more likely. I have observed prolonged acetonuria in a pregnant woman with renal glycosuria. Some patients with renal glycosuria during pregnancy develop true diabetes later in life.

### SUGAR IN THE URINE OTHER THAN GLUCOSE

**Lactosuria:** Lactose appears in the urine in the last stages of pregnancy and during lactation, although it may occur early in pregnancy. Watkins<sup>10</sup> studied intensively the lactose metabolism in women and also describes in detail a method for quantitative determination of lactose in urine. Lactose is a C<sub>6</sub> sugar with a slightly different configuration to glucose. It is a combination of glucose and galactose. Lactose is found in breast-fed children suffering from digestive disorders. It gives a positive Benedict test, a negative fermentation test, a positive mucic acid test and a positive lead acetate test. Lactosuria requires no treatment.

**Galactosuria** is very rare. Bansil<sup>11</sup> mentions 2 cases, one with asthma and the other with a mild hyperthyroidism. Mason and Turner<sup>12</sup> reported a case of galactosuria in an infant and quoted a case of Göppert. Both cases suffered from a disturbance (probably functional) of the liver that lowered the ability of this organ to convert galactose into glycogen without seriously impairing the other functions of the liver. The omission of milk in the diet brought about marked improvement. Galactose gives a positive mucic acid test. Galactosazone crystals have a melting point of 193°.

**Chronic Essential Pentosuria** is a harmless metabolic anomaly. The

urine contains all the time small amounts of reducing substances from 0.2 to 0.6%. Only occasionally the Benedict test may be negative. A study of the urine will reveal pentose (a monosaccharide with C<sup>5</sup>) which can be a d-arabinose or a l-xyloketose. Lasker, Enklewitz and Lasker<sup>13</sup> studied the urines of a large number of different cases of pentosuria reported recently and found l-xyloketose in all of them, although some of the earlier observers (Newberg<sup>14</sup>, Aron<sup>15</sup>, Cammidge and Howard<sup>16</sup>) isolated an inactive arabinose. L-xyloketose in the urine gives a positive Benedict test in a few hours without the application of heat or in ten minutes at 55° (Lasker-Enklewitz test). Pentose is positive with Bial's reagent; it does not ferment with yeast and on treatment with phenylhydrazine it gives characteristic pentosazone crystals with a melting point from 154° to 160°. The daily excretion of pentose is uniform and is uninfluenced by diet or exercise. Margolis<sup>17</sup> has observed that pyramidon (amidopyrine) causes an increase in pentose excretion in pentosuria. Lasker and Enklewitz<sup>1</sup> confirmed it. Where very small amounts of pentose are suspected or where doubt exists as to the diagnosis an increased elimination of pentose can be brought about by pyramidon medication. Enklewitz and Lasker<sup>18</sup> found that pyramidon, antipyrine, borneol and menthol are excreted by normal and pentosuric subjects in the form of glucuronates. The increased pentose excretion observed in pentosuria following the administration of the above drugs they believe to be due to glycuronic acid which is formed in response to these drugs. They have demonstrated that the administration of



glycuronic acid causes a greatly increased elimination of glycuronates in the urine and believe that l-xyloketose arises from glycuronic acid. Schultz<sup>19</sup> suggests that exyloketose is transformed into glycuronic acid in the kidneys.

Pentosuria is more commonly found among children unless it is not recognized until later. It should be looked for in the relatives of the patient, since it is known to be inherited. Lasker believes that pentosuria is inherited as a recessive Mendelian trait, while Schultz<sup>19</sup> believes that it is transmitted as a dominant trait. Most of the cases of pentosuria are among Jews. Many cases are mistaken for renal glycosuria, especially since true diabetes has been observed in the same family. The possibility of finding a rare case when both conditions have been inherited, the diabetes and pentosuria, should be kept in mind. Joslin and his associates<sup>20</sup> mention one case of pentosuria in whom diabetes may also be present. While Moss and Walker<sup>21</sup> reported the first case of diabetes associated with an essential pentosuria. With the aid of Sumner's<sup>3</sup> and Youngburg's<sup>22</sup> methods they were able to determine respectively the total urinary sugar and the total pentose excreted daily. They found that the urinary excretion of the pentose was constant and not influenced by the ingestion of pentose containing fruits, as observed in alimentary pentosuria. Voit<sup>19</sup> claims that he was able to obtain osazone crystals with the melting point of pentosazones in twelve out of fourteen severe diabetics while Enklewitz and Lasker<sup>19</sup> in testing a large number of diabetic urines did not find any pentose. Lasker, Enklewitz and Lasker<sup>18</sup> in reviewing the literature found a total of 119 males

and 51 females, including my cases and their own. In the total there were 8 males and 2 females established as arabinosurias. Among the cases they considered to be xyloketosurias, 46 were males and 22 females. Cases of alimentary pentosuria have been reported by Margolis<sup>17</sup> while Protos<sup>23</sup> speaks of cases of acquired chronic or toxic pentosuria brought on or aggravated by infections. I agree with Lasker et al<sup>18</sup> that the pentosuria probably had been overlooked and was discovered only after the pentose excretion had increased following the administration of drugs.

I have observed 6 cases, 4 patients and 2 relatives (a brother and sister) in whom the pentosuria was discovered when the urines of the immediate family were examined for pentose. In all the cases I have found a positive reducing test in the urine as long as I have followed them. My youngest patient was two years and seven months old when sugar was found in his urine. Two of my patients (a brother and a sister) had been treated with insulin when they came to me. Although at one hospital they had been diagnosed as renal glycosuria, a physician, whom they had consulted later, treated them for diabetes with a diet and insulin. It was difficult to convince the mother that the glycosuria was harmless and that the diet and insulin were unnecessary. While as a rule no symptoms of diabetes are found in these cases, two of my girl patients complained of pruritus vulvae. In fact one was sent to me by a dermatologist who discovered the sugar in the urine. Pentosuria requires no treatment. None of the known cases of pentosuria have ever developed diabetes. They have never shown any disturbance in the

carbohydrate metabolism.

Essential fructosuria is a harmless very rare error in metabolism. Fructose is a ketose just like glucose, a monosaccharide with  $C_6$ . Sachs et al<sup>24</sup> in a review of the literature in 1942 collected thirty-seven reports describing 55 cases of essential fructosuria and added two cases of their own. There were about as many males as females. The percentage of Jews among them was fairly high. The youngest reported patient was two years and seven months old and the oldest 87 years. The largest number of cases were discovered below the age of 40. Diabetes mellitus has been observed in the same family.

Whenever a routine Benedict test is positive for sugar, the mixture of Benedict's solution and urine instead of being heated can be allowed to stand at room temperature overnight. If it becomes positive the presence of 1-xyloketose (ketopentose) and levulose should be suspected since they reduce copper solutions in cold. Fructose can only be discovered if carefully looked for. It is more easily mistaken for renal glycosuria than for diabetes since there are no symptoms of diabetes present and the blood sugar level is normal. Fructose, just like glucose, ferments baker's yeast. It is differentiated from glucose by the reaction it gives with the Selivanoff test. Fructose (levulose) is levorotatory by polariscopic examination in contrast to glucose (dextrose) which is dextrorotatory. After it has been fermented with baker's yeast the urine gives a negative Benedict test, negative Selivanoff reaction and shows no rotation. The urine is sugar-free when the patient is given a fructose free diet and shows sugar on regular diet. On treatment of the

urine with methylphenyl hydrazine, fructosazone crystals are obtained. A glucose tolerance test shows a normal curve while a fructose (levulose) tolerance test gives an abnormal curve which indicates considerable delay in the removal of fructose from the blood stream.

Lasker<sup>25</sup> investigated the families of a number of patients with essential fructosuria and concluded that it is inherited as a Mendelian recessive characteristic. Since the work of Isaak<sup>26</sup> and Ishimori<sup>27</sup> it is generally accepted that the liver converts fructose to glycogen. Some of the authors believe that the liver and others that the kidney is responsible for the faulty metabolism of the fructose.

Sachs et al<sup>24</sup> bring forth the hypothesis that essential fructosuria is due to a failure of the ingested fructose to be broken down to lactic acid. In the normal subject they claim 80% of the ingested fructose is converted to glycogen, while the remaining 20% is being broken down to lactic acid.

Sterkin and Vengerovo<sup>28</sup> showed experimentally that in normal dogs 20 to 30 percent of the ingested fructose is secreted by the liver in the form of lactic acid. Rynbergen et al<sup>29</sup> in 4 cases of fructosuria found that after the ingestion of fructose there was only a slight rise in blood lactic acid and no rise of the respiratory quotient above one. Fructosuria requires no treatment.

#### NON-DIABETIC GLYCOSURIAS WITH HYPERGLYCEMIA

Glycosuria even in the presence of hyperglycemia does not always mean diabetes. A disturbance in the carbohydrate metabolism may be brought about by many causes and

in many ways. It may be of a very short duration or of a more profound and more lasting type.

**Hyperglycemia and glycosuria** may be due to an impairment in the function of the liver to store glycogen, as occasionally observed in liver disease, or to an increased mobilization of liver glycogen brought about by an increased adrenalin secretion resulting from numerous not infrequent causes. It is also known that stimulation of the nerves passing to the adrenal medulla may cause hyperglycemia and glycosuria. The same result is obtained following parenteral administration of adrenalin. Adrenalin causes glycogenolysis in the liver (a breakdown of the glycogen with resulting hyperglycemia and glycosuria). The following glycosurias belong in this group: those due to poisoning with chemical agents such as morphine, ether, carbon monoxide, heavy metals, etc.; in fact all which are due to severe poisonings associated with asphyxia. Emotional glycosuria (fear, fright, pain, anger) is an adrenalin glycosuria. It is produced by a stimulation of the adrenals through the splanchnic nerves.

**Cerebral glycosurias.** Claude Bernard<sup>30</sup> by his famous puncture in the floor of the fourth ventricle was the first to produce hyperglycemia and glycosuria through stimulation of the central nervous system. Marx<sup>31</sup> found the same in connection with an operation on a pituitary tumor. Brugsh, Dresel and Lewy<sup>32</sup> made a more definite localization. They found a particular center of a sympathetic type located in the dorsal nucleus of the vagus (nervus periventricular), the destruction of which causes hyperglycemia. Vonderahe<sup>33</sup> also blames the cerebral

glycosurias on the destruction of the nucleus paraventricularis in the hypothalamus, which he believes regulates the sugar metabolism. According to his hypothesis, the presence of sugar in the blood stimulates this center to activate the production of insulin by the islands of Langerhans. The cerebral glycosuria is probably produced by the way of the adrenals and hypersecretion of adrenalin. Transient glycosuria may follow cerebral hemorrhage, thrombosis, concussion of the brain or embolism. Glycosuria developed in many gun-shot injuries of the skull in the first World War, according to Grafe<sup>34</sup>.

**Alimentary glycosuria** is a glycosuria observed after food intake. It should be considered as diabetes until otherwise proven since normal individuals possess a very high tolerance for carbohydrates, especially in the form of polysaccharides. It may be observed in cases with the "atypical" type of renal glycosuria whose urine shows sugar only off and on. These people show no elevation of the blood sugar and a normal glucose tolerance test. The maintenance of a normal blood sugar is the result of the rate of the removal of sugar from the blood by oxidation and storage being equal to the rate at which sugar is brought to the blood. Intravenous glucose given to a normal person at a rate faster than .85 grams per Kg. body weight per hour causes glycosuria. A normal person can ingest 100 gms. or 1.75 gms. of glucose per kg. body weight with only a slight hyperglycemia and no glycosuria. This is used as a glucose tolerance test. A temporary physiological drop in the tolerance of carbohydrate metabolism can be brought about by starvation, a low carbohydrate and a high

fat diet. It is due to the temporary reduced insulin content and reduced insulin secretion of the pancreas. As a result a transient glycosuria may occur, if the starvation or low carbohydrate and high fat diet is followed by a high carbohydrate intake, and a diabetic tolerance curve may be obtained if a glucose tolerance test is carried out at this time.

# GLYCOSURIAS ACCOMPANYING DISTURBANCES OF DUCTLESS GLANDS OTHER THAN THE PANCREAS

They are hyperthyroidism, hyperpituitarism and hyperadrenocorticism. Glycosuria is not infrequently found in hyperthyroidism. It may be due to the hypersecretion of adrenalin which results in increased glycogenolysis. The hyperglycemia and glycosuria is usually postprandial. The fasting blood sugar is normal. Following thyroidectomy the carbohydrate metabolism returns to normal and the glycosuria disappears. Feeding of thyroid to some individuals may precipitate glycosuria. Simultaneous occurrence of diabetes and hyperthyroidism is not uncommon and should not be overlooked.

Hyperpituitarism and hyperadrenocorticism are known to be frequently accompanied by hyperglycemia and glycosuria. The hyperglycemia and glycosuria in hyperpituitarism comes about through stimulation of the adrenal cortex (adrenotropic hormone) which results in hyperadrenocorticism, the latter causing hyperglyconeogenesis. The adrenal cortex thus contains a hormone, a corticosterone, which is concerned with the production of sugar from protein (glyconeogenesis). Glycosuria in pituitary and adrenal diseases may clear up with the re-

moval of the underlying cause, for instance, removal of a tumor. Young<sup>35</sup> has demonstrated experimentally in dogs that prolonged pituitary administration, with resulting hyperglycemia is followed by real pancreatic injury and pancreatic diabetes. It is thus possible that some human pancreatic diabetes has been preceded by hyperpituitarism. Lukens and Dohan<sup>36</sup> claim that pituitary extract injections in partially depancreatized cats cause diabetes only if hyperglycemia develops. Allen<sup>37</sup> in his early experiments found that in a partially depancreatized dog the prolonged hyperglycemia produced by the Claude Bernard pique caused the development of diabetes.

Campbell, Haist and Best<sup>38</sup> also Lucas and Dohan<sup>39</sup> found that diabetes which is experimentally produced in dogs and cats by repeated pituitary extract injections can be prevented if insulin is administered. The hyperglycemia and glycosuria in hyperpituitarism and hyperadrenocorticism should therefore be treated with diet and insulin in addition to specific treatment in order to prevent, if possible, the development of true diabetes.

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## REFERENCES

- <sup>1</sup> Lasker and Enklewitz: J. of Biol. Chem., Vol. 101, p. 289, 1933.
- <sup>2</sup> Exton: N. Y. State J. Med., Vol. 36, p. 1545, 1936.
- <sup>3</sup> Sumner: J. Biol. Chem., Vol. 65, p. 393, 1925.
- <sup>4</sup> Hawk and Bergeim: P. Blakiston's Son & Co., Phil.
- <sup>5</sup> Marble: Am. J. Med. Sci., Vol. 183, p. 811, 1932.

<sup>6</sup> Goldbloom: Can. Med. Assoc., J., Vol. 24, p. 950, 1924.

<sup>7</sup> Allen, Wishart, and Smith: Arch. Int. Med., Vol. 35, p. 523, 1919.

<sup>8</sup> Williams: Boston Med & Surg. J., Vol. 192, p. 163, 1925.

<sup>9</sup> Kustner: Arch. Gyn., Vol. CXVII, p. 158, 1922; Vol. XVII, p. 282, 1924.

<sup>10</sup> Watkins: J. Biol. Chem., Vol. 80, p. 33, 1928.

<sup>11</sup> Bansi: Klin. Wchnschr, Vol. 11, p. 21, 1932.

<sup>12</sup> Mason and Turner: Am. J. Dis. Child., 50, p. 359, 1935.

<sup>13</sup> Lasker, Enklewitz and Lasker: Human Biol., Vol. 8, p. 243, 1936.

<sup>14</sup> Newberg: Ber. d. deut. chem. Gesell. Vol. 33, p. 2243, 1900.

<sup>15</sup> Aron: Monatschr. f. Kinderheilk. Vol. 12, p. 177, 1913-14.

<sup>16</sup> Cammidge and Howard: Brit. Med. J., Vol. 2, p. 777, 1920.

<sup>17</sup> Margolis: Am. J. Med. Sci., Vol. 177, p. 348, 1929.

<sup>18</sup> Enklewitz and Lasker: J. Biol. Chem., Vol. 110, p. 2, 1935.

<sup>19</sup> Quoted by Joslin et al; Joslin, Root, White, Marble: Treatment of Diabetes Mellitus, Lea & Febiger, p. 728, 1940.

<sup>20</sup> Joslin, Root, White, Marble: Treatment of Diabetes Mellitus, Lea & Febiger, 1940.

<sup>21</sup> Moss and Walker: J. Am. Med. Assoc., Vol. 120, p. 25, 1942.

<sup>22</sup> Youngburg: J. Biol. Chem., Vol. 73, p. 599, 1927.

<sup>23</sup> Protos: Southern Med. & Surg., Vol. 96, p. 154, 1934.

<sup>24</sup> Sachs, Sternfeld, Kraus: Am. J. Dis. of Child., Vol. 63, p. 252, 1942.

<sup>25</sup> Lasker: Human Biol., Vol. 13, p. 51, 1941.

<sup>26</sup> Isaak: Ztschr. f. physiol. Chem., Vol. 89, p. 78, 1914.

<sup>27</sup> Ishimori: Biochem. Ztschr., Vol. 48, p. 332, 1913.

<sup>28</sup> Sterkin and Vengerova: Bull. Biol. et med. exper., URRS., abstracted Chem. Abstr., Vol. 35, p. 6635, 1941.

<sup>29</sup> Rynbergen, Chambers and Beatherwick: J. Nutrition, Vol. 21, p. 553, 1941.

<sup>30</sup> Bernard: Leçons de phys. exper. au College de Frances, Paris, 1855.

<sup>31</sup> Marx: Klin. Wchnschr, Vol. 6, 1927.

<sup>32</sup> Brugsch, Dresel and Lewy: Ztschr. f. exper. Med., Vol. 21, p. 358, 1920

<sup>33</sup> Vonderahe: Arch. Int. Med., Vol. 60, p. 694, 1937.

<sup>34</sup> Grafe: p. 234, Lea & Febiger, Phil., 1933.

<sup>35</sup> Young: New Eng. J. of Med., Vol. 221, p. 635, 1939.

<sup>36</sup> Lukens and Dohan: Endocrin., Vol. 30, p. 175, 1942.

<sup>37</sup> Allen: quoted by Rabinowitch, Diabetes Mellitus, MacMillan Co. of Can., p. 33, 1933.

<sup>38</sup> Campbell, Haist, Ham and Best: Am. p. 222, 1940.

<sup>39</sup> Lukens and Dohan: Science, Vol. 92, J. Physiol., Vol. 129, p. 328, 1940.

## GLYCOTROPIC FACTOR

See Carbohydrate Metabolism.

## GLYCYL BETAINE

A nitrogenous base found in crustaceans, cephalopods and many molluscs.

## GLYOXALASE

An enzyme which catalyzes the conversion of methyl glyoxal to d-lactic acid; requires the presence of glutathione as coenzyme.

## GLYOXYLDIUREIDE

See Allantoin.

## GLYOXYLIC ACID

CHO-COOH, m.p. 98°, present in plant and animal tissues.

## GLYOXYLIC ACID REACTION

See Hopkins-Cole Reaction.

## GLYOXYLIC ACID TESTS

See Duppa-Perkin, Eppinger, Neuberg.

## GMELIN TEST FOR BILE

## PIGMENTS IN URINE

Colored zones, passing from green to blue, to violet, to red and finally to yellow, are obtained when urine is floated on concentrated nitric acid.

Reference: Verdaungs nach Versuchen, Leipzig u. Heidelberg 1826, 60. Zeit. anal. Chem. 6, 501 (1867); 15, 502 (1876). Deut. med. Ztg. 1908, 514. Pharm. J. 26, 686 (1908). Policlinico 29, 537 (1922).

Deut. Med. Wochschr. 1892, 381.

# GOAT'S THORN

See Tragacanth.

# GOITER

Bronchocele; enlargement of thyroid gland or its parts with or without thyrotoxicosis. Types are: (1) non-toxic diffuse goiter, (2) non-toxic nodular goiter, (3) toxic nodular goiter, (4) toxic diffuse goiter. The non-toxic diffuse goiter, or colloid goiter or simple goiter, may be endemic due to shortage of iodine, or pubertic appearing only in puberty, or sporadic due to infection or some other cause. Depending on the type or case one uses iodides, thyroid or resorts to surgical removal. The non-toxic nodular goiter, or adenomatous goiter, is characterized by nodules and pressure symptoms. It may be aggravated by iodides. Toxic nodular goiter, or adenoma with hyperthyroidism, or Plummer's disease, may be concealed for a long time, but requires surgery. Toxic diffuse goiter includes the terms exophthalmic goiter, Graves' disease, Basedow's disease, Parry's disease, hyperthyroidism or thyrotoxicosis. It is a hyperactivity possibly brought on through excess of thyrotropic hormone of the pituitary. Psychic trauma is a prevalent "cause." Focal infection is a minor cause. Increase of at least 25% of basal metabolic rate is considered a conclusive element of diagnosis. Other symptoms are tachycardia (100 to 160 per minute) and eye symptoms. The latter are exophthalmos, or protrusion of eyeballs; von Graefe's sign, a lid-lag of the upper lid behind the move-

ment of the eyeball; etc. Psychotherapy is frequent. Iodides may work great harm as well as help. Radium and X-ray therapy are generally not strongly recommended.

# GOLD NUMBER

A measure of the protective efficiency of lyophilic colloids. It is that weight of the colloid in milligrams which will just fail to prevent a change in color from red to violet when 1 cc. of 10% sodium chloride solution is added to 10 cc. of a Zsigmondy (formaldehyde) red gold solution to which the colloid has been added.

# GOLD REAGENT

See Zsigmondy.

# GOLGI BODIES

Rod-like constituents of certain cells. A coiled tube like organelle seen in many cells.

# GOLODETZ REACTIONS FOR CHOLESTEROL AND OXYCHOLESTEROL

I. A deep blue color is obtained when cholesterol is treated with a few drops of liquid trichloroacetic acid and 1 drop of formaldehyde. II. The addition of 1-2 drops of a mixture of 5 parts concentrated sulfuric acid and 3 parts formaldehyde to solid cholesterol produces a black color.

III. Trichloroacetic acid colors oxysterol green very rapidly; the solution has a red absorption spectrum.

Reference: Chem. Ztg. 1908. 160.

# GONADOTROPIC

Influencing the gonads; usually refers to the anterior pituitary hormones that control gonad secretion.

# GONADOTROPIC PRINCIPLES

The two hormones, Prolan A and



**Prolan B.** Prolan A stimulates male germ cells and ova and ovarian follicles to produce their hormones. Prolan B or the luteinizing hormone stimulates the conversion of the ovarian follicles to corpora lutea and their activity in secreting their hormone (progesterone).

## GONADS

The testes in the male and the ovaries in the female; sex producing glands.

## GONIUM

See Gamete.

## GONORRHEA

An infectious disease due to the gonococcus of Neisser, a gram negative diplococcus. Easily transferred and very persistent, the gonococci may remain latent for a long time after the first course of the disease. The disease has been a great challenge to chemotherapy. Successes have been scored with sulfanilamide, sulfapyridine and sulfathiazole. Artificial fevers have had spectacular results. Irrigations with permanganate and silver nitrate are customary. Mercurochrome has been used and abandoned. There are also gonococcus vaccines. Chronic gonorrhea is called gleet and requires cleaning up of closed foci of infection. Complications of all sorts are found, as gonorrheal arthritis, cystitis, vaginitis, conjunctivitis, ophthalmia neonatorum. Estrogens have been used to treat obstinate cases of gonorrheal vaginitis in children leading to proliferation of an adult, resistant type of epithelium.

See also Fever Therapy, Urology.

## GORLIC ACID

Dehydrochalmogric acid, found

in the oil of gorli seed.

## GOUT

Podagra; a constitutional disease with recurrent arthritic attacks on one or the other big toe and sometimes at the knee or other joints. Heredity has been blamed. Alcoholism is predisposing and often brings on attacks. Uric acid retention in the blood and reduced renal efficiency are shown. The disease may be acute, chronic or irregular. Irregular gout is really only a tendency to gout indicated by such things as itching feet, muscular pains, urinary gravel and calculus. The diet is designed to avoid uric acid formation, e.g. milk diet. Colchicine has been found of value as well as sodium iodide.

## GRAAFIAN FOLLICLE

Cells surrounding the ovum while it is in the ovary.

## GRADIENT

See Field.

## GRAMICIDIN

A neutral polypeptide of a spore-bearing soil bacillus (*B. brevis*) containing a fatty acid unit, alcohol soluble, bactericidal in vivo in very dilute solution; name also applied to a group of such substances; graminic acid; gramidinic acid.

## GRAMIDINIC ACID

See Gramicidin.

## GRAMINIC ACID

See Gramicidin.

## GRAMININ

A fructosan from rye flour. Schlubach and Koenig, Ann. 514, 182 (1942).

## GRAND MAL

See Epilepsy.

## GRANULATION TISSUE

See Wound Healing.

**GRANULOSE**

See Starch.

**GRAPE SUGAR**

See Glucose.

**GRAVES' DISEASE**

See Goiter.

**GRAYING**

See Hair.

**GRAY MATTER**

Part of brain or spinal cord which contains nerve cells; cortex.

**GREEN & BROSTEAUX'S ENZYME SYSTEM**

An enzyme oxidation system of three components, analogous to that of Warburg & Christian. A coenzyme, from yeast or muscle, reacts with lactate in the presence of an enzyme from heart muscle to give pyruvate and reduced coenzyme. The latter, plus the third component, a dye, gives coenzyme and the reduced dye, which is reoxidized by molecular oxygen.

**GRIMMER TEST FOR PEROXIDASES IN MILK**

Raw milk gives an intense brick-red color when treated with 1-2 drops of 0.1% solution ethylhydroperoxide and 2 drops of a solution of guaiacol in 10 cc. alcohol and 90 cc. water. Heated milk shows no color change.

Reference: Milchw. Zentr. 44, 246 (1915). Apoth.-Ztg. 1916, 125.

**GROTE TEST FOR SULFUR IN ORGANIC COMPOUNDS**

Reagent — 0.5 gm. sodium nitroprusside are dissolved in 10 cc. water and 0.5 gm. hydroxylamine hydrochloride and 1 gm. sodium bicarbonate are added. After complete evolution of gas, 2 drops bromine water are added, the solution is filtered and diluted to 25 cc. 5-20 mg. of substance are dissolved

in 3 cc. water and treated with 0.5 cc. reagent and excess sodium bicarbonate; a purple-red color develops within 10 minutes.

Reference: J. Biol. Chem. 93, 25 (1931).

**GROWTH**

Growth is a universal property of living matter by which it tends to increase in amount. However, through the years the volume of living matter on the earth remains fairly constant. The organic mass as a whole and in individuals reaches a maximum of size and efficiency of operation and then breaks down into its elementary constituents. Thus the cycle continues to revolve through the ages with immense biological and economic consequences.

Since growth is increase in size, the methods of measuring growth are: the instruments for determining weight (with due regard to specific gravity) and length of dimensions. For the latter various forms of calipers have been devised including, for microscopic organisms, graduated eye pieces and slides; for macroscopic organisms, sliding and compass calipers. By measuring (preferably the same individual) successively at time intervals, change in size and its rate are determined. Where it is desired to determine the factors involved in growth, the content of water is measured by drying; the role of various foods is determined by using experimental animals (usually rats) fed on stuffs that are complete except for one food element, e.g., a particular protein or vitamin, and measuring the subsequent growth.

Human growth of the body as a whole is determined by repeatedly weighing and by measuring the

dimensions. To measure the differential growth of particular organs various landmarks and special forms of calipers have been devised, as described in works on anthropometry (See Martin, 1928).

Growth may be regarded as of two types: arithmetic (additive) and logarithmic.

Arithmetic growth is shown in the increases of elongated cells or organs that are growing at their ends. Thus the growth in length of long bones in mammals is due to the proliferation chiefly in the direction of the bone axis at the end of the bone and, accordingly, from birth on to maturity the growth is an additive one, the additions absolutely diminishing after puberty.

Logarithmic growth occurs where increase is chiefly that of the organic particles upon which control of the process depends. Since the chemical processes of such particles are largely hydrolytic, oxygen is required for all growth that is due to proliferation of organic particles.

Since growth is so largely a matter of imbibition of water the work of the growth-inciting particles must be control of imbibition, i.e., they are hydrophilic. This matter of relation of water to protein has been discussed in some detail by Gortner ('38, pp. 256-316). These relations are extensive and the role of proteins as "Bausteine" is at bottom due to their hydrophilic properties. The evolution of the protein molecule has made possible the growth of land animals, many developing under limited aquatic conditions. Since the protein is assembled in colloidal particles, the statement of MacDougal ('20 p. 22) puts the case clearly: "It is plainly

evident that growth consists of two fundamental features—hydration of the colloidal material of the plasma and the arrangement of additional material in colloidal structures with the entailed additional capacity for absorbing water." Wrinch ('41, p. 225-229) has developed the theory of protein-water systems according to which the weight of the water molecules associated with the varying numbers of units of a protein molecule may constitute 70, 80, 90, or even 99 per cent by weight of the whole. Apparently the proportion of water associated with a protein molecule may increase during development. Thus we account for the fact that the weight of water in a developing tadpole may increase from 1.03 mg. to 4.51 mg. while the weight of the dry substance increases from .80 mg. to 1.16 mg. Thus the growth of water in this case is not merely arithmetic but logarithmic, since the amount of water depends upon the increasing hydrophilic capacity of the protein molecule which stores it.

In some cases, the cell body contains little water but the polysaccharides and proteins are closely crowded together forming polyhedra and the number of these molecules or aggregates tends to increase logarithmically by aggregation. Animal eggs and most seeds contain comparatively little water and in these cases besides protein there are stores of carbohydrates and fats. Marvin has pointed out the law of increase in number as these polyhedra (hexoctahedra) are formed in successive layers around the central unit. The total number of units,  $S$ , in any aggregation with  $n$  layers is  $S_n = 4n^3 + 6n^2 + 4n + 1$ . This can be reduced to formal identity with the equation of or-

ganic growth,  $\log W = k \log (2t+1) + C$  in which weight is equated against time (Glaser).

Hence a better understanding of growth is obtained by appreciating that it follows the law of aggregation of molecules rather than that of intussusception, as held by T. H. Huxley.

Growth depends not only upon external energy (heat) and oxygen which contributes to internal energy but also upon the addition of foods and especially, in animals, the proteins and their amino acids.

Of the various amino acids taken into the body of mammals certain ones have been shown by experiments (mostly on rats) to be indispensable for growth. These are: lysine, tryptophane, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine, and arginine of which the last can be synthesized in the animal organism, but not at a sufficiently rapid rate to meet the demands of normal growth. Just what role each plays is a matter for future research. It has been shown that lysine is essential for the estrous cycle in animals. The sulphur in methionine is essential to detoxify certain growth-inhibiting compounds that may be taken into the body. Cysteine and glutathione and other sulphhydryl compounds likewise stimulate growth. Also non-sulphhydryl complexes which cause sulphhydryl to be released on contact with proteins may serve indirectly as growth stimulants.

Growth is also determined in large part by internal factors. The same dietary furnished to a large and to a bantam fowl results in different growth due to the hereditary, genetical factors. When a large and a small race of poultry

(Rhode Island Red, and Silkie Bantam) are crossed the hybrid embryos are intermediate in size between pure bred embryos of these races. When chorio-allantoic grafts of limb buds are made from Creeper fowl (characterized by extremely short legs in the adult) the graft shows a similar slow and defective growth as is found in the embryos of this breed. Even when fed in the same institution from early childhood the Norwegain child grows rapidly in stature and size of bones while the Italian child grows more slowly. Again the humerus and the radius of a developing child are supplied by the same blood carrying the same kind of protein molecules and containing the same growth stimulating factors, yet in a particular infant the humerus grew 24 mm. in a year and the radius only 17 mm. Of the food ingested the body, or tissue, selects what its nature requires and rejects most or all of the rest.

The rate of growth shows a vast range in different organisms. Thus the human radius during infancy increases about 17 mm. in one year or 54Å in one second or about one layer of protein plus its accompanying water in two seconds. A sweet potato vine may grow 12 feet in 3 months or 3657 mm. in 8,000,000 seconds or 4570Å in one second, or nearly one thousand times as fast as the human radius. The growth processes are of course quite different in bone and in tissues of cellulose-walled plant cells, but in the growth of both water plays a prevailing part.

Many attempts have been made to express the rate of growth in a mathematical formula. In the case of dividing egg cells the number of cells at any cell generation after the

individual egg (2nd, 3rd, 4th, etc.), or simply  $n$ th is  $2^n$ : thus in the 3d generation 8. But continuous compound interest, which more nearly approximates organic growth, gives at the expiration of the number of time units  $n$ ,  $Y_n = Y_0(1+k)^n$  where  $Y_0$  is size at the start. Or, better still, if  $n$  be infinite,  $Y_n = Y_0 e^{kt}$  where  $k$  is the rate of growth;  $t$  the time of the growth period in convenient units, such as hours or days;  $e$  is the base 2.718. It may be added that, due to complexities in the growth process of animals and plants and to the influence of varying environmental factors upon the course of growth the actual curve rarely follows the formula for a long period.

The formulae of growth rates are based on masses; they give false ideas of growth in the individual. For the latter is characterized by varying rates during the course of development. In fact there is sometimes recognizable an irregular rhythm in the rate of growth. Thus whenever the humerus grows exceptionally rapidly the radius grows exceptionally slowly, and vice versa. Whether this is due to a rhythm in the supply of food, accelerators, and water, or to a rhythm in the utilization of that supplied has not been determined. Such alternating periods of rapid and slow growth have been observed also in tissue cultures.

Rhythmic growth may well be a consequence of the satiation of a growing part that is taking in amino acids rapidly, followed by a cessation of such feeding for a time. It has been shown experimentally that if growth is retarded by cold or starvation, when more favorable conditions ensue it is accelerated

much above the normal growth rate, so that normal weight or size for the given age are attained, and may soon be surpassed.

Rhythmic growth may be due to variation in intake of accelerators of growth, which play an important role in growth processes. This hypothesis is supported by the fact of the prepubertal spurt in human growth which occurs at the time of the maturation of the gonads under the temporary influence of pituitary secretions, especially of its growth promoting factors. This spurt is preceded by some years of slow childish growth and followed by almost complete cessation of growth.

Of the accelerators of growth the most important are the hormones and vitamins. The secretions of the pituitary gland stimulate growth and the effect of these hormones is localized in the proliferating zone of cartilage. Hypophysectomy inhibits skeletal development. Whether there is a special growth hormone produced by the pituitary gland that can be separated from the other pituitary secretions is still a debated question. Prolactin alone will do much to advance growth in a dwarf mouse. The importance of thyroxin from the thyroid gland is shown in cretins where the secretion is insufficient, resulting in dwarfs. Thyroxin has an essential effect on the liver, increasing its size and its complement of protein and leading it to release sugar into the blood (Sternheimer, '39, in *Endocrinology*). It stimulates the proliferation of the cartilage cells at the growth zones of long bones. (Silberberg, '40). Various other stimulators of growth are known among



animals such as l-cystine, dl-methionine, l-cystine disulfoxide, glutathione and SH-compounds in general. Some of these may counteract the growth inhibiting effect of iodoacetic acid (see below).

Plant growth is stimulated by certain plant hormones. Darwin (1881) first demonstrated that the turning of plant stems toward the light was controlled by "some influence which is transmitted from the upper part of the coleoptile of a seedling to the lower part causing the latter to bend." The influence is now recognized as one of the plant hormones known collectively as the growth substance, or auxin. The existence of this auxin is demonstrated by removing the tip from a monocotyledon's (e.g. oat's) coleoptile and sticking it unilaterally on the first leaf, after pulling the leaf part way out of the coleoptile. A growth curvature that turns away from the applied tip (negative) indicates a growth promoting substance; one that turns toward the applied substance (positive) indicates a growth retarding substance in the tip. In place of the tip we may use agar blocks diffused with the growth hormone from the tip; or from other sources. The effective amount of an auxin is exceedingly small. It has been computed that one auxin molecule is active in the formation of  $3 \times 10^5$  glucose residues for the cellulose micellae that build up the plant cell-wall. Auxin is found also in leaves and stems. Auxin usually retards the growth of the root. Auxin acts both on the water and the micellae of the cell walls.

Growth substances (auxins) have been obtained from a variety of plant and animal materials. Rhizo-

pus (bread mold) grown on an appropriate substrate yields a growth stimulating substance named rhizopin, which is probably identical with 3-indole acetic acid (heteroauxin). *Aspergillus* yields a substance that reacts with tryptophane, lysine, leucine, tyrosine and phenylalanine to produce growth stimulators. Urine, after a complex treatment, yields a powerful growth stimulant called auxentriolic acid, or auxin a. Malt, maize oil and some other plant oils yield a growth stimulant called auxenolonic acid or auxin b. Yeast yields heteroauxin. A large number of other compounds have been tested as to growth activators but they are mostly less effective than the foregoing. The degree of activity is measured by applying to the cotyledon particles of lanolin to which the compounds have been added.

In testing the reactions of roots the compounds are added to the soil or injected into the stem. The relation of auxin to root formation is somewhat complicated. Strong solutions of indoleacetic acid may inhibit root growth but weak solutions stimulate it. Indol-butyric acid and naphthaleneacetic acid are also efficient. The results are more striking if sugar or Vitamin B<sub>1</sub> are added as an after treatment; indeed the latter is regarded as a specific growth hormone for roots and is supplied by parts of the plant above ground. Nicotinic acid is an essential growth factor for pea roots. The study of the effects of auxin upon plants is opening up a new field of research into the processes involved in growth.

The various vitamins that affect growth of mammals are: thiamin (Vitamin B<sub>1</sub>), which is believed to



catalyze the transformation of pyruvic acid and is thus essential in intermediary metabolism; riboflavin (Vitamin G), which catalyzes the oxidative processes in the body tissues; Vitamin D, which promotes the growth of the long bones; Vitamin C (or ascorbic acid), essential to later stages of growth of mammals; and Vitamin A essential to the growth of young rats. After exhaustion of stores already in the body, on a diet lacking in Vitamin A growth ceases.

In vertebrates, at least, certain mineral elements are necessary to the upbuilding of the mineral-containing organs of the body. Such are iron, as in the blood; calcium, as in the teeth and bones; phosphorus also required by bone.

In many of the above cases it is not general growth but that of specific essential organs that is affected.

Organic growth has this remarkable property that, after a period of logarithmic advance it reaches a point of maximum rate, whereafter it begins to decrease in a fashion that is roughly a mirror image of the former increase and eventually leads to complete cessation. The equation of this process of limiting of growth is given by Brody ('27, p. 66) as  $dw/dt=k(A-W)$ ,  $W$  being weight at a given instant;  $A-W$  growth still to be made under proportionately constant or relative rate of growth ('37, Growth, I:60). After growth ceases the body reaches its maximum of efficiency. After a shorter or longer period, deterioration sets in and eventually death ensues. This cessation of growth is not due to some changes in the cells of older organisms, for such cells grow equally

well in tissue cultures as embryonic cells. It is probably due to failure of growth stimulus.

The mechanism of growth inhibition has been inadequately studied. It has been found that high dietary cholesterol has an inhibitory effect on the growth of rodents. There are certain sulfur-containing amino acids which detoxify certain added foreign substances that would interfere with growth of rats; but a deficiency in such acids may result from the feeding of methylcholanthrene, benzpyrene and diphenyl with a consequent inhibition of growth. Varying amounts of polycyclic, particularly carcinogenic, hydrocarbons produce similar growth inhibition. This growth inhibition in immature rats may or may not be due to the same causes as inhibition at maturity.

Not only is there an inhibition of growth of the body as a whole but also a specific inhibition of growth of particular organs. Thus growth of the cranium is inhibited earlier than that of the maxilla and mandible, or that of the extremities. The epithelium of the vagina undergoes rapid growth before ovulation as soon as the corpus luteum is developed, following ovulation, this epithelial growth is inhibited, and it can be shown experimentally that the luteal secretion is the effective inhibiting agent.

Cancer is a reaction of susceptible tissue cells to growth stimulating agents, external or internal. Too often in the past there has been a failure to consider the quality of the tissue or organism. Among growth stimulating agents are cholanthrene derivatives (e.g. 4:10-dimethylene 1:2-benzanthracene);

benzpyrene; 2-methyl-3:4—benzphenanthrene; O-aminoazotoluene and derivatives; — the variation in potency of derivatives of this compound, some of which are wholly inactive, is a striking fact. The estrogens, such as estrone benzoate, injected into mice cause tumors. When such estrogen is applied together with 3:4 benzpyrene the tumors appear earlier and develop more rapidly.

Inhibition of tumors induced by a carcinogenic compound is effected by the same carcinogenic compound. The action is not strictly proportional to the carcinogenic power. Thus 1:2:5:6-dibenzanthracene is more inhibitory than 3:4-benzpyrene. On the other hand, a series of non-carcinogenic compounds tested under the same conditions gave no inhibition of tumor growth. The carcinogenic compounds slow up the growth of the treated animals so that reduction of tumor growth may be a result of inhibition of growth of the body in general.

In certain tumors (e.g. Rous sarcoma) a virus is the apparent carcinogeneus agent. If 3:4-benzpyrene is added intensified and generalized growth follows. So long as the pH of the tumor is kept below 7 virus activity remains high, but is suddenly lost at about 3 at which pH the protein molecule splits, an indication of a collaboration between virus and protein in the production of the tumor.

Ultraviolet radiations accelerate the formation of tar cancer in mice; the tar products are believed to sensitize the skin to such rays, perhaps by concentration of cholesterol. Yeast cells injured by ultraviolet radiation produce a substance

that promotes growth. The same radiation may produce abnormal growths on the human skin. Yet X-rays are used effectively in inhibiting tumor growth. The same agent may stimulate or inhibit growth depending upon its intensity above or below the threshold of the tissue subjected to the agent.

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# REFERENCES

- Brody, S., et al, '26-36. Growth and development with special reference to domestic animals. I-XXXIX.
- Cook, J. W. and E. L. Kennaway, 1938. Chemical compounds as carcinogenic agents. *Am. J. Cancer*, XXXIII: 50-97.
- Gortner, R. A., 1938. *Outlines of Biochemistry*, 2nd edition, 1017 pp., N. Y.
- Hammett, F. S., 1929. The chemical stimulus essential for growth by increase in cell number. *Protoplasm*, VII: 297.
- Huxley, J. S., 1923. *Problems of Relative Growth*. N. Y.
- Jensen, P. Boysen, 1926. *Growth Hormones in Plants*. Transl. by G. S. Avery and P. B. Burkholder. N. Y. 268 pp.
- MacDougal, D. T., 1920. *Hydration and Growth*. Carnegie Inst. of Wash'n. Publ. No. 297, 176 pp.
- Martin, R., 1928. *Lehrbuch der Anthropologie*. Jena. 1816 pp.
- Robbins, W. J., S. Brody, A. G. Hogan, C. M. Jackson and C. W. Greene, 1928. *Growth*. New Haven. 189pp.
- Peterson, W. H., 1941. The merging of growth and vitamins. *Biol. Symposia*, V:31-43.
- Robertson, T. B., 1923. *The Chemical Basis of Growth and Senescence*. Phila.
- Sherman, H. C., and S. L. Smith, 1922. *The Vitamins*. N. Y.
- Thompson, D'Arcy W., 1942. *Growth and Form*. 2d. Ed. N. Y.
- Went, F. W. and K. V. Thimann, 1937. *Phytohormones*. N. Y. 294 pp.
- Wrinch, D., 1941. The native protein theory of the structure of cytoplasm. *Cold Spring Harbor Symposia on Quantitative Biology*, IX:218-235.
- Growth: A Journal for Studies of Development and Increase*. Vols. I-IV and Supplements.

**GROWTH FACTORS,  
SYNTHESIS OF**

See Genetics, Biochemical.

**GROWTH HORMONE**

A principle produced by the anterior lobe of the pituitary gland, which has control over height and growth in general.

**GROWTH, INHIBITION OF**

See Plant Growth Hormones.

**GRUBER TEST FOR INDICAN  
IN SERUM**

A mixture of 3 cc. concentrated hydrochloric acid, 1 cc. serum and a small amount of isatin is boiled for 30 seconds, cooled, shaken with 1 cc. chloroform to an emulsion, separated by centrifuging and the chloroform layer washed with 10 cc. 10% sodium hydroxide. Violet color indicates pathological amounts of indican.

Reference: Wiener med. Wochschr. 82, 1253 (1932).

**GSH**

Glutathione.

**GSSG**

Oxidized glutathione.

**GUAIACOL**

Ortho-methoxyphenol, a constituent of guaiacum resin, beechwood tar; employed in lumbago, etc.

**GUANASE**

An enzyme associated with guanine (2-amino-6-oxypurine). It deaminates guanine to xanthine (2, 6-dioxypurine).

**GUANIDINE**

Iminourea, occurs in small amounts in vetch seedlings.

**GUANIDINE TESTS**

See Ackerman, Sakaguchi, Sullivan.

**GUANINE**

2-amino-6-oxypurine; an amino purine occurring in nucleic acids.

**GUANINE GOUT**

A disease of the pig due to the absence of guanase resulting in the failure of guanine to oxidize to xanthine and uric acid.

**GUANOPHORE**

Cell containing yellow pigments originating from guanidine derivatives; iridocyte.

**GUANOSINE**

A nucleoside consisting of one molecule of guanine and one molecule of d-ribose. May be considered as derived from guanylic acid through the loss of phosphoric acid. The linkage is from the C<sub>1</sub> of the sugar to N<sub>7</sub> of the guanine.

**GUANYLIC ACID**

A mononucleotide consisting of one molecule of phosphoric acid, guanine, and d-ribose.

**GUARANINE**

See Caffeine.

**GUILHON TEST FOR IRON  
PIGMENTS IN LIVER**

A few drops of potassium ferrocyanide solution are added to 1 drop of fresh liver pulp which has been stirred with 0.5 cc. hydrochloric acid; the presence of hemosiderin is indicated by a Prussian blue color.

Reference: Compt. rend. soc. biol. 115, 376 (1934).

**GUM ACACIA**

See Gum Arabic.

**GUM ARABIC**

A mixture of several gums, the best being that obtained from Acacia Senegal; it is usually completely soluble in water.

**GUM DAMMAR**

An oil soluble gum, which acts as an efficient stabilizer of water-in-oil emulsions.

**GUM RESIN**

See Oleoresins.

**GUMS**

Carbohydrate derivatives consisting largely of glycoside-like polymers of hexoses and pentoses, together with complex acids.

**GUM TRAGACANTH**

See Tragacanth.

**GUNZBURG TEST FOR HYDROCHLORIC ACID IN GASTRIC JUICE**

Equal volumes of gastric juice and of reagent (solution of 2 gm. phloroglucinol and 1. gm. vanillin in 40 cc. alcohol) are evaporated in a porcelain dish; a red residue indicates free hydrochloric acid.

Sensitivity—1:0000-2:0000.

Reference: Deut. Med.-Ztg. 8, 931. Biochem. Zeit 1912, 45, 49. Pharm. Weekblad 1927, 304.

**GURWICH RAYS**

Mitogenetic rays; penetrating rays from live matter.

**GUTZEIT TEST FOR ARSENIC**

One gm. of zinc is placed in a large test tube with 4-5 cc. dilute sulfuric acid and 1-2 drops copper sulfate solution and the tube loosely plugged with cotton. The cotton is moistened with a drop of lead acetate and a strip of filter paper impregnated with silver nitrate is put over the mouth of the tube. Darkening of the paper shows arsenic.

Reference: Pharm. Ztg. 24, 263 (1879). Zeit. anal. Chem. 11, 62 (1872); 30, 116 (1891). J. Soc. Chem. Ind. 25, 509 (1906). J.A.C.S. 38, 1280 (1916).

**GUVACINE**

$C_6H_9O_2N$ ; an inactive alkaloid of the Areca nut; prisms m.p. 271-272°.

**GUYOT BIOLOGICAL REACTION FOR BLOOD**

The chromogen of fungus *Boletus cyanescens* is used as the reagent. To destroy oxidases, the cut fungus is boiled with water and macerated with 60% alcohol for 48 hours; the solution is exposed to sunlight and filtered. 2 cc. of a solution of blood in 50 cc. water is superposed with the reagent and treated with 1-2 drops hydrogen peroxide; a greenish zone turning blue is obtained. The test is only indicative, not specific. Bloods altered by carbon monoxide and leukocytes do not give this reaction.

Reference: Schweiz. Apoth.-Ztg. 59, 281 (1921).

**GYMNOSPERMS**

Flower bearing plants which produce naked seeds in cones or berries, usually evergreen, e.g. Coniferae as pine, spruce, larch, juniper.

**GYMNOTUS (EEL)**

See Protozoa.

**GYNECOGENIC SUBSTANCES**

See Estrogens, Synthetic.

**GYNESIN**

See Trigonelline.

**GYNOCARDIA OIL TEST**

See Lifschutz.

**GYNOCARDIC ACID**

$C_{17}H_{33}COOH$ , m.p. 67.5°, a constituent of chaulmoogra oil.

## H

### HAAS FLAVOPROTEIN

A bottom yeast enzyme qualitatively of the same kind as the Warburg-Christian enzyme (q.v.).

### HAEM

The non-protein portion of the hemoglobin molecule,  $C_{34}H_{32}O_4N_4Fe$ , with the iron in the ferrous state; ferroporphyrin; is also the base of other haemochromogens differing from hemoglobin with respect to their protein component.

### HAEM-

See spelling with hem-.

### HAEMATOIDIN

Bilirubin as it occurs in bruises.

### HAEMATOPOIESIS

Blood formation by liver, bone marrow, spleen, lymph glands; haematosis.

### HAEMATOSIS

See Haematopoiesis.

### HAEMERYTHRIN

Red respiratory pigment of certain annelid worms; contains iron.

### HAGEDORN-JENSEN REAGENTS AND METHOD FOR DETERMINING BLOOD SUGAR

(1) To precipitate protein 0.1N sodium hydroxide and 0.45% zinc

sulfate solution are mixed in the proportion of 1:5 shortly before use.

(2) 10.6 gm. ignited sodium carbonate and 1.65 gm. potassium ferri-cyanide are dissolved in 1 liter of water.

(3) 50 gm. sodium chloride, 5 gm. potassium iodide and 10 gm. zinc sulfate are dissolved in water and diluted to 200 cc.

(4) 3 cc. of iron-free glacial acetic acid are diluted with water to 100 cc.

(5) 1 gm. soluble starch dissolved in 100 cc. saturated sodium chloride solution.

(6) 0.7 gm. sodium thiosulfate in 500 cc. water are standardized against a solution of 0.3566 gm. potassium iodate in 2 liters water. 0.1 cc. of blood is dealbuminized by warming with 6 cc. of (1), filtered and the residue washed 3 times with 3 cc. portions of water. Filtrate heated in boiling water bath for 15 minutes with 2 cc. of (2) and then treated with 3 cc. of (3). Mix with 2 cc. of (4), use 2 drops of (5) as indicator and titrate with (6).

Reference: Biochem. Zeit. 135, 46 (1923); 137, 92 (1923); 146, 538 (1924); 157, 172 (1925). J. pharm. chim., 11, 78 (1930).



### HAHN OXINE REAGENT

The reagent (8-hydroxyquinoline) in 5% alcoholic solution is used to determine aluminum, zinc and magnesium; to separate aluminum or zinc from alkaline earth and alkali metals and to separate magnesium from the alkali metals.

Reference: *Zeit. angew. Chem.* 39, 1198 (1926). *Zeit. anal. Chem.* 71, 123 (1927). *J.A.C.S.* 50, 1900 (1928).

### HAIR

Hair is the term applied to a form of cutaneous outgrowth which normally occurs in all mammals, but in members of no other class. The "hairs" of birds, amphibians, fish and plants are so different from the hairs of mammals that there is no question of confusion nor much likelihood of close relationship. Mammalian hairs are prevailingly sub-cylindrical or flattened aggregates of keratinized cells, probably exclusively ectodermal in derivation, although a few statements in the literature are to the effect that they also have a collagenous component derived from mesoderm. The presence of any such connective tissue derivative has not been generally confirmed.

**Development.** Each hair shaft, followed from tip to base, furnishes a record of a period of activity in the follicle from which it grew, and the series of successive hairs from the same follicle reveals the periodicity and changes in such activity. All hair follicles are believed to arise before or shortly after birth, the time of their appearance varying with the species and the prospective size of the follicle. In each case a strand of cells grows obliquely down from the epithelium into the corium and differentiates into the outer and inner epithelial

sheaths which in turn become surrounded by a moderately firm connective tissue sheath. A specialized connective tissue papilla projects into the bulb-like dilatation at the end of the epithelial down growth. Cells of the bulb immediately above this papilla multiply and become converted into the hair shaft whose tip is pushed further and further out by basal growth. This small region is of critical importance in studying factors affecting hair growth. Sebaceous glands usually arise from the more distal part of the follicle, and in many species sweat glands do also. In nearly all follicles an arrector pili muscle runs from beneath the epithelium to the inferior wall of the follicle beneath the sebaceous gland.

**Arrangement.** The first follicles to appear in a prospectively hair covered area are usually rather uniformly spaced. They often appear to be in lines, but at times it is difficult to determine whether this appearance is real or only apparent. There is need for further interpretation of such geometrical arrangements as actually occur. That they have a phylogenetic significance with respect to an earlier scaly covering may be doubted. The first follicles to appear produce the largest hairs, probably throughout life. Secondary, tertiary and subsequent follicles are progressively smaller and apparently bear more or less definite spacial relation to the earlier ones already present. Since in some of the common laboratory animals many of these follicles do not appear till after birth, the possibility of their control is open to experimental test.

Aside from the groupings of follicles just referred to there are other more intimate associations.



Two kinds of "hair tufts" are recognized, the term being used in a special restricted sense. In the so-called "true tufts," or compound follicles, characteristic groups appear, each consisting of one main hair and several categories of smaller hairs which arise from small papillae that have branched off from the main follicle and for the most part are enclosed in its sheath. There is usually only one set of sebaceous and sweat glands to each tuft, but occasionally one of the larger accessory hairs has a gland associated with it. "False tufts" arise when the skin around two or more independent follicles becomes depressed with the result that the hairs involved all emerge from the same pit, which may appear superficially to be the mouth of a single follicle. This latter condition can sometimes be observed in the human forearm. The two types of tufting are generally supposed to be distinct, but there seem to be some doubtful or transitional cases. A somewhat similar appearance, not to be confused with the foregoing, is produced when a hair that is about to be shed still persists in a follicle from which its successor also protrudes. In such cases the old hair is easily removed, the new one is more firmly fixed and often brighter in color. Finally, those follicles which open separately on the surface often become secondarily pulled together in groups by surrounding masses of connective tissue fibers which gradually increase in volume during development. On the human scalp these groups, which include from one to eight hairs, increase in number during the third quarter of prenatal life and then tend to become stabilized. The groups are not altogether dis-

tinct and may be composed of different follicles at different depths in the corium.

**Hair Follicles.** Even small follicles frequently have large sebaceous glands and relatively strong arrector pili muscles. Larger follicles have thicker walls, and in many cases a good nerve supply. In such cases the hair and its follicle may serve as a kind of passive sense organ, especially when the follicle is made more tense by contraction of its muscle. Follicles of true tactile hairs, which occur in all animals except man, fall roughly into three categories, all of which are richly supplied with nerve terminations. In the most elaborate of these the inner connective tissue sheath is modified into an erectile body called the corpus spongiosum pili. At its upper limit there is a more or less completely circular sinus. These most highly specialized follicles are supplied by striated fibers from the neighboring musculature and are therefore under some degree of voluntary control, whence the designation active tactile hairs. Other tactile hair follicles have only smooth muscles and are called passive, some with and some without a circular sinus.

**Types of Hair.** Hairs themselves vary in size from the barely visible "down hair" or vellus of man to the immensely enlarged protective spines of hedgehogs and spiny anteaters. In form they range from short fusiform to greatly elongated shafts which in cross section may be circular, elliptical, prismatic or irregular in outline. Human hairs are commonly considerably flattened. Most hairs taper toward both ends but tend to be fairly uniform throughout their greater extent. Fluctuations may occur,

somewhat irregular in hairs from the human scalp, or regularly as in certain hairs of lower mammals in which the soft basal part of the shaft is tipped by a thicker, firmer, but usually pointed terminal portion. The broad, scale-like tips of *Ornithorhynchus* hairs afford an extreme example of this type of deviation from uniformity in diameter of the shaft. In gross structure the shaft consists of cuticle, cortex and frequently medulla. The cuticle is a thin layer of translucent scales, usually without pigment. These scales may be coronal, each completely encircling the shaft or, more commonly, imbricated, their size bearing an inverse relation to the diameter of the shaft. Both types may occur in the same individual, coronal scales being limited to the smallest hairs. The cortex which constitutes the bulk of the hair shaft consists of cells generally so highly keratinized as to give the whole a translucent homogeneous appearance. In and among these cells may be a greater or less amount of pigment. In the medulla, on the other hand, cells are more loosely arranged and for this reason as well as because of the air that is likely to be present among them, they show differences in diffraction from the rest of the shaft. The medulla is usually absent at the tip and base and may be present or absent through varying extents of the shaft. In general large hairs are more likely to have medullas than small ones. Inasmuch as there are almost perfect transitions between the largest and smallest hairs, attempted classifications found in special treatises are all more or less unsatisfactory. In man the larger conspicuous, pigmented hairs are called terminal hair, the fine vellus is often referred to as down or

fuzz, and intermediate forms are called transitional. Terminal hair varies in character in different parts of the body and is variously designated, e.g. capillus, cillia, tragus.

Physical and Chemical Properties. In its physical and chemical properties hair seems to share most of the characteristics common to other keratins. Analyses reported in the biochemical literature are numerous but the results, while showing good agreement on the whole, are still too diverse in some respects to justify a survey by one not a specialist in the field. The occurrence of well over a dozen amino acids in hair seem to be well established, and it would appear that at least some among them (e.g. histidine, lysine and arginine) tend to show constant ratios with reference to each other. The cystine content is relatively high in almost all hair, especially human (15+%), and probably higher in that of men than of women. It is also possibly higher in hair of adults than in that of growing children, although some authors report no differences associated with age, sex or color of hair. The nitrogen content of hair is reported as about 15% and that of sulphur is around 5%, practically all of the latter being accounted for by the cystine and methionine, except in camel's hair where there is a larger sulphur content than is needed for these amines. Other elements reported in hair include lead, arsenic and antimony. It has been maintained that these latter elements are "excreted" through the hair. This is open to doubt, particularly in the case of lead. Lipoids, in the hair of young rats, amount to about 4.5% of which 11.9% is cholesterol. In human hair there are more lipoids than in the subcutaneous tissue, but less than

in the skin. The proportion of cholesterol to total lipoids varies in the hair of rat, cat, rabbit and dog, but the absolute amounts are said to be about the same, .55-.57%. The non-chemical student of this subject is likely to regret that, however excellent the analyses, the selection of the original material has often been less critical than might seem desirable. Furthermore, the difficulty in adequately separating and evaluating the pigmentary components is unfortunate because these may represent products of an essentially independent system.

The question of molecular organization and consequent physical properties of keratins, particularly those of hair, has been vigorously pursued for the last ten or twelve years by an active group of investigators lead by W. T. Astbury of Leeds. It appears from their analysis of X-ray photographs that hair or wool can be stretched by an amount equal to about 2% of its original length without injury or permanent deformation of the keratin. In cold water it can be stretched by an amount equal to about 2% of its original length without injury or permanent deformation of the keratin. In cold water it can be stretched considerably more than that and yet return to its original condition. In steam or other softener the hair can be stretched still more, usually to twice its original length. For each medium in which it is tested the breaking point seems to be the same whether the tension is increased slowly or rapidly. Hair stretched to the limit in steam is found to undergo internal changes, which are believed to be in the nature of an extension of a normally folded polypeptide grid, made possible by the elimination of certain

cross bonds resulting in conversion of the keratin from an alpha to a beta form. In this way hair or wool can be "set" in its new state; but if when first stretched to its full extent in steam it is allowed to suddenly contract in the same medium, it may then become even shorter than originally. Subsequently (the original linkages now being destroyed), stretching to twice its length in cold water is followed by complete recovery. The extensive findings in this field are of great theoretical interest and of value in the textile industry, to the practical hair dresser, and in the laboratory where it may be desirable to restore distorted hairs to their original form. The relation of keratin molecules in the different cells which go to make up the hair shaft is a matter of interest needing further study.

Shape of the cross section of a hair shaft is not closely associated with the form of the hair, as has often been supposed. The hair index (lesser diameter divided by the greater), while useful in a descriptive way, does not necessarily afford a clue to the curliness of the shaft except that hairs with a high index are often straight and those with a low index are sometimes, but not always curly. In this connection the relation of the two major axes to each other is of importance. Since hair is somewhat hygroscopic when dry, moisture tends to correct purely mechanical deformations that may have been induced by combing, by the hair's own weight, etc. In a number of abnormalities of the hair shaft such as trichorrhesis, monilithrix and pili torti, the shaft fluctuates somewhat regularly in diameter and breaks easily at the nodes. X-ray examinations of samples of the two latter anomalies are

said to show no peculiarities in the molecular structure, from which it is concluded that these deviations are essentially "histological."

**Pigment.** Pigmentation of hair, particularly in laboratory and domestic animals, has been studied with much success by geneticists. The histogenesis and chemistry of hair pigments have also been studied, but with considerably less success. Two different kinds of coloring are commonly recognized: a diffuse 'stain' which is usually non-granular and in tones of yellow or red, and a clearly particulate type which occurs in tones of brown, ranging from 'black' to very light 'yellow.' The latter are all generally considered to be true melanins. There is less certainty about the former which, however, may not be so distinct as sometimes supposed. Probably all colors and patterns in mammalian hair are due to various combinations of these pigments, whose effects are often modified by structural characteristics of the hair or by other extraneous factors. The interrelation of the two possible classes of pigment has long been a matter of interest. In certain respects they behave independently in heredity but they are both influenced in the same direction, although not always to the same degree, by factors for albinism and dilution. One of the most suggestive recent attacks on their chemical relations is that of Arnow who reports that "if red human hair is extracted with boiling 0.1N hydrochloric acid, a red brown pigment is obtained in solution. This pigment has the physical properties of a pigment prepared by the mild oxidation of a dopa melanin in alkaline solution. It is suggested that the distinctive color

of red hair is due to the presence in such hair of an oxidation product of melanin." Such an hypothesis has much to commend it and seems to be in accord with some of the facts established by genetics. Whether or not it will be found to agree with all of them remains to be seen. If granular melanin is a precursor of the red-brown pigment, it might be questioned why such genes as those for dominant white should sometimes suppress the black before they do the yellow. Results thus far obtained by the perhaps too violent methods of biochemists may ultimately require confirmation by genetic and microchemical tests.

Melanin granules in hair resemble, at least superficially, those in feathers, but it has not been determined whether or not their genesis is the same. In birds, it now appears, all the melanin producing cells are derived exclusively from the neural crest of the embryo. These pigmentoblasts which migrate from their original site near the mid-dorsal line to their ultimate position in the feather germ constitute an essentially separate and independent system which determines the color and, for the most part, the pattern of the feathers. Whether or not the same is true for mammals is still uncertain, but Rawles found that neural crest tissue of early mouse embryos transplanted into the coelom of white Leghorn chick embryos produced pigmentoblasts which migrated away from the graft into the peritoneum. Reed demonstrated by skin transplantation in young mice that pigment and possibly other cells migrate from the host into the border of the graft and enter some of the hairs. This in a measure con-

firms and extends the early work of Carnot et Deflandre and of Loeb who maintained that dark pigment migrates from graft to host skin in autoplasmic transplants on the ear of guinea pigs, a finding which some later investigators have questioned. In light of the implications of these findings the graying of hair possibly becomes a little less puzzling. If the pigment producing cells of the hair are of a different nature and genesis from those that constitute the rest of the shaft, it is less surprising that the residual stock of them in the follicle should show a different and characteristic susceptibility to adverse influences such as X-rays, and perhaps even have a different rate of senescence. Koller following the earlier work of Onslow reports that in the rabbit, extracts of most colored skins give strong melanin reaction with dopa while under the same conditions extracts from dominant white skin do not form melanin, and if added to extracts of dark skin completely inhibit pigmentation. Extracts from recessive white skin form no pigment with dopa but when mixed with other extracts do not prevent them from doing so. These and other interesting oxidation phenomena parallel the genetic behavior of hair color in the same strains. Some investigators have not been able to get clear-cut results in other species with similar genetic behavior.

**Differentiation of Growth Center.** The various properties of the shaft must almost all be determined within a very short radius of the tip of the papilla, and in consequence special interest centers around this region. The greatest proliferative activity occurs just above the papilla which through its rich blood

supply functions in conveying nutrient to the growing bulb and also possibly serves as an inductor for such growth. It has been established in other connections that destruction of the papilla terminates further hair growth, but the more difficult feat of bringing a papilla to bear on undifferentiated ectoderm has probably not been accomplished. In hair, as to an even greater extent in feathers, epithelial cells show a high capacity for undergoing morphological and probably chemical changes at some distance (measured in cell diameters) above the basement membrane. Such changes are primarily determined by the constitution of the cells themselves but are influenced by factors brought to bear at the moment of differentiation. These latter factors seem to be predominantly physical and humoral. Free nerve endings often occur in the inner hair sheath but it is doubtful if they play any direct role in the activity of the growing bulb. It is often claimed that the shape (as shown in cross sectional view) is determined by the inclination of the papilla or the curvature of the follicle through moulding of the soft, incompletely cornified root. While these factors may very well be of some importance, it seems more likely that the form taken by the drying shaft as it emerges from the follicle is chiefly due to differentials in the character and arrangement of the cells of which it is composed. Variations between cortex and medulla are sufficient to show that almost any degree of difference in compactness and looseness of cells is possible in the hair bulb. When and how pigment comes into existence in the hair follicle is a histological problem that calls for further study. Whether intra-

cellular granules are autochthonous or are deposited within the cells by migratory pigmentophores, as similar granules are deposited in feather cells, and the source of the inter-cellular granules are questions still to be answered.

**Cyclic Activity of Follicles.** So far as is known hair production is never continuous in any one follicle. The usual activity, as measured by the length or volume of hair produced in a unit of time, takes the form of an S-shaped curve which begins slowly, increases rapidly to the maximum which is maintained fairly constantly for the greater part of the growth period, and then slows down to a complete stop. Following cessation of growth the bulb itself cornifies and the papilla regresses. During the ensuing resting period the exposed part of the hair usually fades appreciably and is likely to suffer to some extent from attrition. Toward the end of the period the papilla shows renewed activity, a new bulb forms around it and the old bulb gradually rises to the surface and finally falls out, but often not till the new hair is projecting from the mouth of the follicle. The relative duration of growth and rest periods varies with the species and with the type of hair. In many animals the growth period is relatively short and the rest period long. There may be seasonal moults during which replacement of hair is, extensive, but even in such cases there is some replacement at other seasons. In a careful year-around study of the guinea pig, Dawson found regenerating hairs during every month except August. Pulling out a growing hair generally results in a new hair forming somewhat sooner than it otherwise would. Commonly hair

replacement is more or less continuous with little or no synchronism between follicles. This is the case in man. In the rodents certain zones or areas often moult independently of other regions, producing a pattern effect which is apparent because of the difference between the new and the faded old hairs. This tendency is often revealed following shaving or depilation of an area in the rat or mouse, when new hairs may come in quickly over part of the area but not till much later over other parts. The phenomenon, which is a normal occurrence, has been mistaken for the result of experimental procedures. Although early successions of hair are quite regular in the rat (Butcher) at older ages it becomes difficult to get specimens that parallel each other and are really suitably matched to serve for experimental and control subjects.

**Control of Follicular Activity.** Attempts to regulate physiological processes in the follicle have rarely met with much success. That in some animals large numbers of hairs fall out and are replaced simultaneously naturally suggests that factors outside the follicles are involved, and that it should be possible to bring them under control. In other mammals, including man, hair follicles often show a high degree of autonomy, maintaining their own length of cycle and growth rate little influenced by variations in any ordinary factors. The writer has observed several follicles on one of his fingers for a period of about twenty years during which time there has been no apparent tendency for the cycles of different follicles to become synchronized, even when the average lengths differ by only a few days. Nevertheless there can be little



doubt that variations in hormones, vitamins and nutritional factors exert some, although perhaps mostly an indirect influence on hair growth and pigmentation. Under such circumstances the difficulty already mentioned of securing wholly satisfactory control animals is an especially serious handicap.

The often destructive effects of X-rays have long been known. X-ray treatment, depending on its intensity, may produce an area of permanent alopecia, temporary alopecia followed by graying of the new hair, by complete and normal recovery, or even perhaps by slight stimulation. Numerous authors have pointed out that many hair stimulants affect the hair only as they affect the skin or general status of the individual. For example, Peck found that injection of pyrrol bodies causes increased pigmentation in the rabbit, but hastened to add that so do numerous other factors including injury to the skin. He concludes that the most important factors are general growth stimuli. It has often been assumed that cutting or shaving the hair hastens its growth, a question debated by Trotter and Seymour, the latter claiming that there is such an effect, the former explaining the apparent results as due to a statistical fallacy contingent on the fact that in any region some hairs are always approaching the end of their cycle with consequent slowing of growth rate, thus tending to depress an average covering several days as compared with one for only a single day. The need for study of individual hairs rather than groups which may be in different phases is thus emphasized. There are several factors whose absence results in inadequate production of pigment. At least one of these,

associated with the B complex, affects the pigmentation without influencing hair growth (Morgan and Simms). There is, however, according to these authors, an associated dermatitis and both it and the graying are corrected by extracts of adrenal cortex and thyroid, so it would appear that in the final analysis this type of graying may be due to a hormonal disturbance. Others have inferred on experimental grounds that the graying factor is distinct from any known component of the B complex. Finally Free reports that there are different kinds of graying, one of which can be produced by deficiency of iron, copper and manganese. Cures for the different types, as might be expected, are not the same.

**Sex Differences.** Differences in hair associated with sex have been studied rather extensively. Apparently the actual number of hair follicles in the two sexes is about the same, but the types of hair they produce may vary appreciably as in the mane of the lion or the beard of man. In many other species there seems to be no noticeable difference in the peltage of the two sexes. Zawadowsky seems to have shown that in some species where the sexes differ in color, as in an antelope (*Portax picta*), the male pattern and coloring develops only in the absence of female hormones, which is reminiscent of what occurs in some birds. But for the most part no such associations have been detected. For some purposes it is convenient to classify hair of different regions into three classes: that which is uninfluenced by sex, that which is ambosexual, and that which may be considered a true secondary sexual character. It is

not to be supposed that these categories are at all clearcut. In man, hair of the forehead, orbital region, and ordinarily other parts of the body is apparently uninfluenced by presence or absence of either sex gland. Follicles that produce such hair could be placed in the first class. Other hair, such as axillary and pubic, is about the same in both sexes but fails to reach full development following early gonadectomy. Traits of this sort are called ambosexual (Champy). The beard and much of the hair on the limbs and trunk, including the hypogastric region (often confused with the pubic) belongs in the class of secondary sexual characters, in the sense that the degree of development is normally different in the two sexes. In what appears to be a well controlled experiment on an adult man, Whitaker found a marked increase in the length and weight of terminal hair over a small abdominal region to which testosterone propionate was applied, and in the dog Gardner finds evidence of an inhibitory effect on hair growth by estrogens. Danforth was unable to detect any effect of either testosterone propionate or theelin applied to hair follicles of the finger. Almost complete series of transitions in hair types can be found in either sex, which weakens the evidence that regulation is primarily or prevalingly hormonal. While striking effects do sometimes appear in ambosexual and secondary sexual hair of individuals suffering from tumors of the suprarenal cortex, the condition of the hair seems in general to be not so much a matter of specific stimuli as the manifestation of normal tendencies which may be more or less influenced by the milieu. This does not imply any question as to the accuracy of

numerous reports in the literature which, when taken together, indicate that under certain conditions almost any hormone may have some relation to hair growth. An especially interesting bit of evidence in this connection is supplied by Hamilton who has made rather extensive observations on castrate men and boys. It has been known at least since the time of Aristotle that eunuchs seldom become bald, but Hamilton reports that with castrates of the proper age who, judging from their male relatives, would have become bald under normal conditions, the injection of testosterone propionate is followed rather promptly by incipient, or later advanced, baldness, while those who on the same grounds would probably not have naturally become bald rarely show this tendency. When "caused" by the injection of testosterone the baldness can be relieved by its withdrawal. Hamilton's findings are in line with data from entirely different sources which indicate that baldness is a hereditary sex-limited trait. It would appear from the data at present available that baldness, if the genes for it are present, expresses itself only under normal conditions, which, in the male, involve the presence of a certain amount of male hormones. Occurrence or non-occurrence of baldness, then, is no more indicative of the hormonal condition of the individual than of his genetic constitution.

**Genetic Factor.** Genetic factors concerned in hair form and color have been studied extensively, and in many cases with great success. Dozens of distinct hair colors and patterns are known in the mouse, and their occurrence and frequency in various crosses can be predicted

with great accuracy. Symbols indicating the genes for color (and other traits) in the mouse are now "official" so that mice with hair of a desired type can be ordered from a supply house by formula, much as chemicals can. The length and form of hair as well as temporary and permanent alopecias of many forms and laboratory mammals have been shown to be under hereditary control within closely defined limits. The genetics of hair traits is especially well known in the rat, rabbit, sheep and guinea pig, and there is much detailed information on the ox, dog, cat and horse. In human heredity these factors have not all been determined and analyzed with equal precision but the evidence indicates that they are of the same order as those of lower mammals. Among the latter, there is little evidence that perfection of new strains involving variations in hair color has been associated with much change endocrinologically.

**Summary.** By way of summary it may be inferred from the available evidence that the hair follicle is a highly individualized structure with an unusual degree of autonomy. During its development it acquires characters which are primarily dependent on the genetic constitution of the animal and the region of the body involved. These characters may undergo some change with age but on the whole are remarkably insensitive to extra follicular influences. Nevertheless, it has been adequately demonstrated that under suitable conditions certain follicles may respond in some measure to mechanical stimuli, to different kinds of radiation, to vitamins, to hormones and to nutritional states. These responses, however, appear to be for the

most part general and non-specific. The hair that grows from the follicle serves as a record of follicular activity.

**Literature.** The literature on hair is extensively and widely scattered. Published papers appear prevalently in journals covering the fields of anatomy, biochemistry, genetics, physiology and medicine (especially dermatology), but there are also many from other sources including experimental biology, natural history and physics. Few good bibliographies can be cited. Landauer (in *Zeitschrift für induktive Abstammungs- und Vererbungslehre*, Bd. XLII, 1926) lists some 600 titles, and in *Physiological Reviews*, vol. 19, 1936, Danforth adds references to some of the more recent papers. Some of the articles cited in the latter list, especially those by Astbury, Conitzer, Hausman and Trotter, will serve as key sources to much of the fundamental data and to further titles. What is probably the majority of current papers deal with the chemical and physical properties of the hair shaft, factors involved in experimental graying, possible effects of estrogens and androgens, follicular development and autonomy.

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#### HAIR INDEX

See Hair.

#### HAIRS, PLANT

See Hair.

#### HAIR TUFTS

See Hair.

#### HAIRS, TACTILE

See Hair.

#### HALDEN REACTION FOR VITAMIN D

A solution of vitamin D in benzene, chloroform or ether is treated

with 5-10 drops of a 0.1% alcoholic pyrogallol solution and evaporated on the water bath to a few tenths of a cc. 2-4 drops of a freshly prepared 10% absolute alcohol solution of aluminum chloride are added and the solution reheated; a deep violet color appears in a few minutes.

Reference: Naturwissenschaften 24, 296 (1936). Nature 137, 909 (1936).

### HALICYSTIS

See Bioelectric Potentials, Proto-plasm.

### HALIDES, ORGANIC, TEST FOR

See Sah-Ma Reagent.

### HALISTERISIS

Demineralization of bone, especially with age.

### HALLOCHROME

A red pigment of the skin of the annelid worm, *halla*; also obtained from tyrosine by action of tyrosinase.

### HALOGENS, TEST IN ORGANIC COMPOUNDS

See Beilstein.

### HAMAMELOSE

Aldohexose with branched chain, obtained from a glycoside with gallic acid of the bark of *Hamamelis* tannin.

### HAMMARSTEN REACTION FOR CHOLIC ACID

The powdered acid is shaken at room temperature with 25% hydrochloric acid in a closed flask; the color changes from yellow to yellowish-green and, after a few hours, to bluish-violet. An absorption spectrum is shown about the D line.

Reference: Zeit. physiol. Chem. 61, 495 (1909).

### HAMMER CREATINE TEST

A very small quantity of creatine

is added to 2.5 cc. of butter culture (for acetylmethylcarbinol and diacetyl) in a test tube 0.5 in. in diameter; a volume of 40% sodium hydroxide equal to the volume of the culture is added and shaken. A red color is obtained, its rate of development and intensity at the surface are closely correlated with aroma and desirable flavor of cultures.

Reference: J. Dairy Sci. 18, 579 (1935).

### HANUS SOLUTION FOR DETERMINATION OF IODINE NUMBER

13.2 gm. of iodine are dissolved, with gentle heating in 1 liter of glacial acetic acid, the solution cooled to 23° and the iodine content of a 25 cc. portion determined by titration with 0.1N sodium thiosulfate. A quantity of bromine, equal to that of the iodine present, is added to the rest of the solution and the solution, protected from light, is kept in glass-stoppered bottles.

Reference: Zeit. Untersuch. Nahr.-u. Genussm. 1901, 913.

### HAPLOID

Pertaining to a cell having half the number of chromosomes that the somatic cells have; e.g. gametes.

### HAPTEN

A substance which, although not antigenic, reacts in vitro with antibodies. By combination with protein hapten can often be converted into antigen.

### HARDENING OF THE ARTERIES

See Arteriosclerosis.

### HARDEN-YOUNG ESTER

Fructose diphosphoric acid.

### HARDY-SCHULTZ LAW

The generalization that the precipitating effect of a colloid by an ion is a function of its valency (approximately as the square of the concentration of the divalent, cube of the concentration of the trivalent ion, etc.).

### HARMALNE

An alkaloid of seeds of *Peganium harmala*, associated with harmine and harmalol.

### HART TEST FOR $\beta$ -HYDROXYBUTYRIC ACID IN URINE

Add 20 cc. water and a few drops of acetic acid to 20 cc. of urine and boil to a volume of 10 cc. Dilute to 20 cc. and divide into 2 portions. To tube 1 add 1 cc. hydrogen peroxide, warm for 1 minute and cool. To each tube add 0.5 cc. glacial acetic acid and a few drops of a freshly prepared aqueous solution of sodium nitroprusside. Stratify both solutions with 2 cc. concentrated ammonia and, after standing 4-5 hours, compare the two tubes. Tube 1 shows a purplish-red contact ring if  $\beta$ -hydroxybutyric acid were present originally while the second tube shows either no color or a faint brown contact ring due to much creatine.

Reference: *Am. J. Med. Sci.* 137, 869.

### HAUPTZELLEN

Cells of the stomach responsible for secretion of rennin and pepsin; chief cells.

### HAUSMANN'S METHOD

A method for the quantitative study of the hydrolytic products of proteins, distinguishing between ammonia nitrogen, basic nitrogen, non-basic nitrogen and humin (or melanin) nitrogen. The ammonia nitrogen is ob-

tained on the distillate over magnesia, the basic nitrogen on a phosphotungstic acid precipitate, the non-basic nitrogen on the filtrate of the above precipitate, and humin nitrogen on the black material which separates on hydrolysis with strong acids.

### HAY FEVER

Pollinosis; an allergic catarrhal inflammation of the eyes and the upper respiratory passages due to wind-borne pollens (spring, summer and fall types). It is quite close to non-allergic types like vasomotor rhinitis and allergies toward animal proteins and foods. Ephedrine by mouth and epinephrine by injection are used along with acidosis and calcium therapy.

### HAZELOPP DETERMINATION OF CYSTEINE

2 cc. of a chloroform solution of o-benzoquinone are shaken with 2 cc. of a hydrochloric acid solution of cysteine. The chloroform layer is separated and dried over anhydrous sodium sulfate and the color compared with a solution of 1.25 gm. cobalt acetate in 10 cc. water to which has been added 1 cc. 9% ferric chloride solution. Color is equivalent to 2 mg. cysteine. Cystine does not give the reaction.

Reference: *Chim. ind.* 33, 325 (1935).

### HEART FAILURE

See Creatine and Creatinine Metabolism.

### HEAT INCREMENT

See Calorogenic Effect.

### HEBIN

A name suggested for the gonad-stimulating hormone of the anterior pituitary.



**hederin**

The crystalline saponins of the ivy, hydrolyzable to arabinose, rhamnose and hederagenin.

**Hehner number**

The weight of the acids not volatile with steam obtained by saponification of five grams of fat.

**helenien**

A carotenoid found in flowers of *Helenium*. Its structure is  $\beta$ -alpha'-carotene-3-3'-dioldipalmate.

**helicorubin**

A red respiratory hemochromogen found in mollusca and crayfish liver, composed of heme and a globin. It closely resembles hemoglobin.

**helicin**

The glycoside of salicyl aldehyde, made by oxidizing salicin (q.v.).

**heliotropism**

Phototaxis; heliotaxis; phototropism; reaction to light stimulation.

**Heller test for albumin in urine**

A white ring is formed, even at dilutions of 1:40000, when urine is carefully floated on concentrated nitric acid.

Reference: Arch. phys. path. Chem. 5, 169. Zeit. physiol. Chem. 12, 215; 44, 170; 81, 80. Med. Record 67, 538 (1905). Münch. med. Wochschr. 1916, 1782. Pharm. Ztg. 1917, 38.

**hemagglutinins**

See Immunological Phenomena.

**hematin**

The non-protein portion of the methemoglobin molecule,  $C_{34}H_{33}O_6N_4Fe$ , with the iron in the ferric state; ferriprotoporphyrin; is the component of other para-haematin than methemoglobin differing

from it in respect to the protein component.

**hematoblast**

Parent cell of red blood corpuscle found in liver or bone marrow; blood platelet; erythrocyte; microcyte.

**hematogenesis**

Blood development.

**hematoidin**

See Bilirubin.

**hematopoietic principle**

A substance found in normal livers, which is responsible for prevention of anemia. Its structure is not known, although it may be an enzyme, formed from an "intrinsic factor" of the gastric mucosa, and an "extrinsic factor" of certain foods.

**hematoxylin**

$C_{16}H_{14}O_6 \cdot 3H_2O$ ; a pigment from logwood; it is a reduced alpha pyrone derivative.

**hematuria**

Blood in the urine due to a multiplicity of causes and showing both macroscopically and microscopically. The causes may be renal, ureteral, vesical, urethral, prostatic, infectious, malarial, leucemic, parasitic and drug injury. Essential hematuria is attributed to renal causes. These may be (1) nephrolithiasis, or stone in the kidney, (2) renal tumors (carcinoma, sarcoma, hypernephroma, embryoma), (3) acute parenchymatous nephritis, (4) tuberculosis of the kidney, (5) pyelitis, pyelonephritis or pyonephrosis, (6) hydronephrosis, (7) polycystic kidney, (8) general injury to the kidney from falls or blows, (9) infarction of the kidney. Amongst the drugs which may cause hematuria are large doses of quinine, methamine,



salicylates, cantharides, phenol, arsenic.

Many chemical tests have been devised for the detection of blood in the urine, e.g. benzidine, Heller's, Rosenthal's, Struve's, besides microscopic and spectroscopic tests. Therapy in causal. See also Hemoglobinuria.

## HEME

Hematin.

## HEMICELLULOSES

Polysaccharides combined with sugar acids of the uronic type, more susceptible of hydrolysis, but unrelated to celluloses.

## HEMIN

$C_{34}H_{32}N_4O_4Fe\ Cl$ ; Hematin with the Cl on the central iron replacing the OH.

## HEMOCHROMOGEN(S)

(1) The union of heme with a variety of nitrogen-containing compounds, e.g. proteins, bases (pyridine, picoline, etc.), amino acids, ammonia, cyanide, etc. While the term hemochromogen was previously restricted to the reduced form, the term parahematin being applied to the oxidized form, it is now employed for both forms. Example: Pyridine ferri- and ferrohemochromogen.

(2) Compounds of heme (haem) with proteins and bases, the combination being with two molecules of base; can combine with CO and oxidize readily to parahematin.

## HEMOCONIA

See Chylomicrons.

## HEMOCUPREIN

A crystalline blue copper protein of red blood cells, m.w. about 35,000, containing 0.34% Cu which may have enzymatic activity.

## HEMOCYANIN

The respiratory chromoprotein of the cephalopods analogous to hemoglobin. The metal copper is associated with it, causing the compound to be light blue in the oxidized state and colorless in the reduced state. The weight of evidence is against the prosthetic group being a porphyrin.

## HEMOCYTE

Blood corpuscle.

## HEMOERYTHRIN

A respiratory chromoprotein found in worms. It appears to contain a porphyrin which is not mammalian hematin.

The red pigment of the blood that transports the oxygen to the tissues. It is composed of a porphyrin "hematin" and a protein "globin." The red pigment, also called oxyhemoglobin, gives up oxygen to the tissues and becomes purplish reduced hemoglobin. The iron of the porphyrin nucleus is in the ferrous state, and forms an oxidation-reduction system with methemoglobin.

## HEMOFUSCIN

The yellow pigment of the blood in old bruises.

## HEMOGLOBIN, REDUCED

The purple respiration "catalyst" of the blood stream. It absorbs oxygen from the air changing to red oxyhemoglobin. See Hemoglobin.

## HEMOGLOBINS

See Chromoproteins.

## HEMOGLOBIN TEST

See Lison.

## HEMOGLOBINURIA

Hemoglobin in the urine. If due to an autohemolysis it is paroxysmal hemoglobinuria. Hemoglobin is found in the urine also due

to malaria, hemolytic icterus, internal hemorrhage and other diseases accompanied by hemolysis, as scurvy, purpura, scarlet fever, typhoid fever, malaria, yellow fever, syphilis, septicemias, hemolytic anemias, hemolytic jaundice, etc. Various tests have been devised, e.g. Donath-Landsteiner test for hemolysis on incubation.

See also Hematuria.

### HEMOLYSINS

See Microbiology, Immunological Phenomena.

### HEMOLYSIS

The diffusion or exudation of hemoglobin from red blood cells into the surrounding blood, sometimes due to destruction of the cell wall, sometimes to osmotic pressure.

### HEMOLYSIS OF CELLS

See Permeability.

### HEMOPHILIA

See Hemorrhagic Diatheses.

### HEMOPROTEINS

Chromoproteins.

### HEMORRHAGIC DIATHESES

Constitutional states predisposing to hemorrhage. Under this head comes the concept of purpura, a group of diseases in which bleeding occurs under the skin and the mucous membrane, scurvy and hemophilia, a hereditary abnormality limited to males and transmitted through the female, marked by prolonged bleeding because of the very slow coagulability of the blood. In scurvy the bleeding is due to weakness of capillary walls. The purpuras are described as thrombocytopenic and non-thrombocytopenic

(angiopathic). In the former the number of blood platelets is decreased, the bleeding time is prolonged and the coagulation is normal; in the latter there is no decrease in blood platelets. The former includes essential and secondary forms. Essential purpura hemorrhagica is present in both sexes; secondary purpura is associated with tumors, anemias, leukemia, severe infections and overdoses of X-rays and radium. The non-thrombocytopenic purpuras include mild forms (purpura simplex) and anaphylactoid purpura, arthritic purpura (Schönlein's disease) and visceral purpura (Henoch's purpura). Secondary forms occur in infectious diseases (septicopyemia, scarlet fever, smallpox, black measles, cerebrospinal fever, typhus, rocky mountain fever, leukemia, syphilis); toxic purpura due to snake venom, numerous drugs or to cachexia of carcinoma, tuberculosis, Hodgkin's disease and even old age, or to neuritic complications; hepatic purpura; and purpura due to mechanical blocking of veins and bruising.

Special tests have been devised to determine bleeding time, e.g. Ivy technique of blotting blood drops at intervals from a standard puncture; and coagulation time, e.g. Peterson and Mills method by observing a column of blood in a standard capillary tube.

The treatments are causal.

### HEMOTOXIN

See Immunological Phenomena.

### HENDERSON-HASSELBACH EQUATION

The expression

$$\text{pH} = \text{pK}_a + \log[\text{Salt}]/[\text{Acid}]$$

Where  $K_a$  is the ionization con-

stant of a given acid; used in estimating the approximate pH of a solution of a weak acid in the present of one of its salts. It may also be used judiciously to estimate buffering action by replacing the salt concentration by the concentration of the anion provided the salt is well ionized and the acid is not.

### HENOC'S PURPURA

See Hemorrhagic Diatheses.

### HEPARIN

A compound found in the blood, and formed largely in the liver. It maintains the fluidity of the blood by preventing prothrombin from being converted into thrombin.

### HEPATIC FUNCTION TEST

See Rosenthal Reagent.

### HEPATITIS

See Liver Cirrhoses.

### HEPATOCUPREIN

A copper protein from liver containing 0.34% Cu but different from haemocuprein; may be an enzyme.

### HEPATOFLAVIN

An early name for riboflavin.

### HEPATOTOXINS

Liver poisons, as chloroform, yellow phosphorus, heavy metals, etc.

### HEPTOSE

Any monosaccharide with the formula  $C_7H_{14}O_7$ .

### HERCYMINE

A betaine corresponding to histidine which accompanies it; present in many fungi.

### HERING REACTION FOR ERGOT

By extraction with petroleum benzene about 2 gm. of finely powdered ergot is freed from oil and

an infusion prepared from 1 gm. of extracted ergot in 20 cc. water and 1 drop hydrochloric acid. 4 cc. of the filtered infusion are treated with 1 drop of ammonia and shaken vigorously with 10 cc. ether. 5 cc. of the clear ether layer are floated on about 2 cc. concentrated sulfuric acid; a cornflower-blue zone forms in a few minutes just below the interface. Reference: Apoth. Ztg. 43, 91 (1934).

### HERMAPHRODITE

A person or animal who has or appears to have both male and female characters.

### HEROIN

See Diamorphine.

### HERTER REACTION FOR INDOLEACETIC ACID

A reddish-violet color is produced when a solution of indoleacetic acid is treated with a mixture of hydrochloric acid and a 2% solution of p-dimethylaminobenzaldehyde.

Reference: J. Biol. Chem. 1908, 238, 253.

### HERZFELD TEST FOR GLUCOSE IN BLOOD

An alkaline solution of methylene blue is decolorized by glucose. Solutions—(a) 1:1000 methylene blue solution; (b) 20% potassium hydroxide solution; (c) 10% metaphosphoric acid solution.

Reference: Zeit. physiol. Chem. 77, 420 (1912).

### HERZOG REAGENT FOR LYSINE AND ORNITHINE

Lysine and ornithine form addition products with phenylthiocarbamide which, on treatment with concentrated hydrochloric acid, form hydantoins crystallizable from acetone-alcohol mixture.

Reference: Zeit. physiol. Chem. 34, 525 (1902).

**HESPERIDIN**

A flavone of Vitamin P.

**HETEROAUXIN**

A member of the auxins, or plant hormones. It is  $\beta$ -indoleacetic acid. It has a potency of 25,000,000 A.E.

**HETEROGONY**

The dissimilar growths of a part from the whole body; allometry.

**HETEROLYSIS**

See Wound Healing.

**HETEROSIS**

Hybrid vigor; the greater vigor of some hybrids as compared to either parent.

**HETEROTROPHIC BACTERIA**  
See Microbiology.

**HEXAMETHYLENETETRAMINE**

Hexamine; formin; urotropin; a urinary antiseptic.

**HEXAMINE**

See Hexamethylenetetramine.

**HEXOKINASE**

A component of zymase that converts hexoses to a more reactive, probably an enol, form.

**HEXOSANS**

$(C_6H_{10}O_5)_x$ ; polysaccharides derived from hexoses by loss of water. Examples are cellulose, starch, glycogen.

**HEXOSE**

Any monosaccharide with the formula  $C_6H_{12}O_6$ ; with the pentoses make up the most important groups of the monosaccharides.

**HEXOSDIPHOSPHATASE**

See Enzymes, Non-Proteolytic.

**HEXOSEMONOPHOSPHORIC ACID**

Alpha-fructose-6-monophosphoric acid; a product associated with hexose metabolism. See Carbohydrate Metabolism.

**HEXOSEMONOPHOSPHORIC ENZYME**

The pyridinoprotein enzyme containing coenzyme II which catalyzes the oxidation of glucose-6-phosphate to 6-phosphogluconate. Found in red blood corpuscles and yeast.

**HEXURONIC ACID**  
l-ascorbic acid.

**HEXYLRESORCINOL TEST**  
See Revillon.

**HIPPULIN**

$C_{18}H_{20}O_2$ , m.p.  $283^\circ$ ; an estrogenic hormone found in pregnant mare's urine; it has one alicyclic double bond more than estrone, and one-seventh its potency.

**HIPPURIC ACID**

Glycyl benzoic acid;  $C_6H_5CO-NH-CH_2COOH$ ; an acid found in horse urine, also found as a detoxication product to remove benzoic acid from the body.

**HIPPURIC ACID TEST**  
See Dehn-Scott.

**HIPPURICASE**

An enzyme that splits off the acid radical, particularly the benzoyl radical from certain peptides containing natural amino acids. The optimum pH is 6.8 to 7.0.

**HIRSCHFELD TEST FOR PUS IN PATHOLOGICAL BODY FLUIDS**

Reagent — mixture of equal volumes of an aqueous solution of dimethyl-p-phenylene diamine hydrochloride and of 1%  $\alpha$ -naphthol

solution in 70% alcohol or 1% potassium hydroxide. When the reagent is floated on a purulent secretion, an indophenol-blue color is obtained.

Reference: Deut. med. Wochschr. 1917, 1620.

## HIRUDIN

A proteose of the salivary gland of the leech; it is an anti-coagulant.

## HISTAMINE

$\beta$ -imidazole ethyl amine. A poisonous amine formed by bacterial action on histidine. It exerts a very powerful depressive action on the blood pressure, and stimulates gastric secretion of acid.

## HISTAMINE TESTS

See Asmacher, Koessler-Hanke, Van-Itallie-Steenhauer.

## HISTIDASE

An enzyme occurring in the liver, which supposedly breaks open the imidazole ring of histidine.

## 1-HISTIDINE

$C_6H_9O_2N_3$ ;  $\beta$ -imidazol- $\alpha$ -aminopropionic acid; m.p.  $277^\circ$ ; i.p. 7.21; an indispensable basic amino acid. It dilates capillaries and increases their permeability and on injection causes a stimulation of the parietal cells of the stomach to secrete HCl. See Gastrin.

## HISTIDINE METABOLISM

The nature of the metabolism is not known other than as follows. The organism is capable of utilizing large amounts of histidine, and also of synthesizing it, or of substituting imidazolacetic acid or carnosine for it. It is a precursor of uric acid and allantoin.

## HISTIDINE TESTS

See Kossel-Patten, Pauly, Kap-

peler-Adler, Koessler-Hanke, Zimmermann.

See Genetics, Biochemical.

## HISTIDINURIA

The appearance of large amounts of histidine in the urine, as in pregnancy. It is accompanied by the disappearance of histidase from the liver, and has been explained on the theory that it ensures an adequate supply of histidine for the embryo.

## HISTOCHEMISTRY

Histochemistry is a sector of biochemistry devoted exclusively to the biochemistry of tissues. Gersh defines the aims of histochemistry as (1) to define quantitatively the relations of chemical substances located intracellularly with those in their immediate environment and (2) to determine quantitatively the relations of intracellular chemical entities to the morphological organization of the cell.

The dynamics as well as the complexity of the cell constituents, along with a lack of good quantitative analytical methods, militate against rapid progress in this field. For example, microincineration fixes the relative positions of inorganic materials, but can in no way hope to present a picture of change and diffusion unless long series of samples are taken. For most purposes, however, tissues have to be fixed to prevent diffusion due to death of the cell. Only the most common elements, e.g. calcium, magnesium, potassium and chloride, carbonate, phosphate, have been studied extensively. Amongst the heavier elements, arsenic and lead take the lead. Iron and copper claim delicate methods. Besides microincineration mentioned above there are the supplemental techniques of using X-

rays and the spectroscope. In this field one might include any and all micromethods for determining vitamins, hormones and enzymes whose biological effects are great for small amounts of substances. These also depend on skillful micromanipulations of single cells or portions of cells. For some problems histochemical procedures seem to be very imperative, e.g. the site of secretion of hydrochloric acid in the stomach, bile secretion in the liver, the *modus operandi* of the kidney, the localization of vitamins and enzymes. Histochemists have been particularly interested in fine reactions for the cytochromes, vitamin C, the nucleic acids, cytoplasmic constituents, thyroxine, pepsin, various lipases and amylases.

Reference: I. Gersh, *Physiological Reviews*, 21: 242-266 (1941).

## HISTOHEMIN

An earlier name for cytochrome.

## HISTOLOGY

The study of the microscopic structure of tissues.

## HISTONES

In the American Classification of proteins, the Histones are simple proteins, soluble in water, insoluble in very dilute ammonia, soluble in very dilute acids and in solutions of the alkali metal hydroxides. On hydrolysis the basic amino acids predominate. The yield precipitates with solutions of other proteins, which are probably coacervates.

Examples: globin of hemoglobin and scombron in mackerel spermatozoa.

## HISTOZYME

An old name (1881) for hippuricase.

## HOFFMAN DETERMINATION OF PENTOSE

The test substance is hydrolyzed by steam distillation with 12-20% hydrochloric acid; 1-5 cc. of distillate are neutralized, to phenolphthalein, with 50% sodium hydroxide, treated with 0.5 cc. aniline and 4 cc. acetic acid and diluted to 10 cc. After standing for 15 minutes in the dark, the furfural is determined colorimetrically against standard furfural solution. The test is positive even in concentrations of 0.00005%.

Reference: J. Biol. Chem. 73, 15 (1927).

## HOFMEISTER REACTION FOR CREATININE AND KYNURENIC ACID

The addition of phosphotungstic acid to a solution of creatinine acidified with nitric acid results in the formation of a yellow crystalline precipitate.

A precipitate of rhombic plates is obtained upon the addition of mineral acid and phosphotungstic acid to kynurenic acid.

Reference: Zeit. physiol. Chem. 5, 67, 71.

## HOFMEISTER SERIES

See Lyotropic Series.

## HOLO

Prefix meaning "whole," "entire," "complete."

## HOLOZYMASE

Zymase together with all its activators.

## HOLOZYMES

See Zymase.

## HOMATROPINE

Mandelyl-tropeine; an artificial alkaloid used to dilate pupil of eye (mydriatic activity).



## HOMEOSTASIS

A tendency to uniformity or stability in the normal body states of the organism.

## HOMO-

Prefix meaning "similar."

## $\alpha$ -HOMOCHELIDONINE

$C_{21}H_{23}O_5N$ ; stout colorless needles, m.p. 170-171°; alkaloid found with  $\beta$ -homochelidonine in *Adlumia*, *Bocconia*, *Corydalis*, *Dicentra*, *Sanguinaria* and other plant genera.

## $\beta$ -HOMOCHELIDONINE

Monoclinic prisms, m.p. 159°-160°; alkaloid usually found with  $\alpha$ -homochelidonine in *Adlumia*, *Bocconia*, *Corydalis*, *Dicentra*, *Sanguinaria* and other genera. Closely related to cryptopine in structure. In mammals causes narcosis, temporary fall in blood pressure, convulsions and paralysis of the motor centers and sensory nerves.

## HOMOCYSTEINE

$SH(CH_2)_2\cdot CHNH_2\cdot COOH$ ; an intermediate in the in vivo transformation of methionine to cysteine.

## HOMOCYSTINE

$(COOH\cdot CHNH_2\cdot CH_2\cdot CH_2S)_2$ ; an intermediate in the in vivo transformation of methionine to cystine.

## HOMOGENETISIC ACID

2, 5-dihydroxyphenylacetic acid. Found in the urine in alcaptonuria, as a product of a hereditary inability to completely oxidize tyrosine and phenylalanine, of which it is a normal metabolic intermediate.

## HOMOGENETISIC ACID TEST

See Garrod.

## HOMOIOTHERMIC

Pertaining to animals that can

maintain a constant body temperature against the environment.

## HOOKWORM DISEASE

See Ankylostomiasis.

## HOPKINS-COLE REAGENT FOR TRYPTOPHANE

Tryptophane solution, made 5% with respect to sulfuric acid, is treated with the reagent (solution of 10 parts mercuric sulfate in 90 parts 5% sulfuric acid). The tryptophane, precipitated quantitatively, may be obtained pure by successive treatment with hydrogen sulfide and baryta water.

Reference: J. Physiol. 27, 418 (1901).

## HOPKINS-COLE TEST FOR PROTEINS

Having found that the Adamkiewicz reactions depends upon the presence of glyoxylic acid in the glacial acetic acid used, the authors use the former acid directly. The test solution is mixed with an equal volume of glyoxylic acid and stratified with concentrated sulfuric acid; tryptophane containing proteins form a reddish color at the interface.

Reference: Proc. Roy. Soc. (London) 68, 23 (1901). J. Biol. Chem. 1907, 11, 289; 6, 51 (1909).

## HOPKINS REACTION FOR INDOLE

A red color is produced when indole is treated with glyoxylic acid and concentrated sulfuric acid. Sensitivity—1:500000.

Reference: J. Physiol. 35, 88 (1906). Zent. inn. Med. 1913, 268.

## HOPKINS REAGENT FOR GLUTATHIONE

Treatment of glutathione in dilute sulfuric acid solution with freshly prepared cuprous oxide results in the formation of a precipitate.

Reference: J. Biol. Chem. 84, 272 (1929). Biochem. J. 25, 614 (1930).

**HOPKINS TEST FOR LACTIC ACID IN STOMACH CONTENTS**

5 cc. concentrated sulfuric acid containing a little copper sulfate are added to a few drops of stomach contents, heated for 2 minutes, cooled, and a small quantity of thiophene added. A cherry-red color indicates lactic acid.

Reference: J. Physiol. 35, 808.

**HORDEIN**

A prolamine found in barley seed.

**HORDENINE**

p-hydroxy-phenyl-ethyl-dimethylamine, m.p. 117°, obtained from barley seed and has weak pressor action.

**HORDENINE TEST**

See Labat.

**HORMONE**

A chemical which is secreted by an endocrine gland in small amounts directly into the blood stream and greatly influences the functions of some specific organ and frequently of the body as a whole.

**HOUSSAY ANIMAL**

See Blood Sugar.

**HOVEY-HODGINS TEST FOR GLYCERIN IN THE PRESENCE OF ETHYLENE GLYCOL**

3 cc. of freshly prepared 10% aqueous catechol and 6 cc. concentrated sulfuric acid are added to 3 cc. of test solution and boiled for 0.5 minutes; a blood-red color formed at about 140-145° indicates glycerin. Ethyl alcohol, ethylene glycol and diethylene glycol give no color: distinctive colors are obtained with other polyhydric alcohols.

Reference: Ind. Eng. Chem. Anal. Ed. 9, 509 (1937).

**H-STROPHANTHIN**

See Pseudostrophanthin.

**H-SUBSTANCE**

See Itching.

**HUBL SOLUTION FOR DETERMINING IODINE NUMBER**

(1) solution of 30 gm. mercuric chloride in 500 cc. 90% alcohol.  
(2) solution of 25 gm. iodine in 500 cc. 90% alcohol. The reagent is stable in the mixed form but should not be used until 48 hours after mixing.

Reference: Zeit. anal. Chem. 25, 432 (1886); 39, 654 (1900). Chem.-Ztg. 1902, 554.

**HUMATURE**

Scale devised by averaging the dry bulb temperature and the percentage humidity to express the thermal demands of the environment of the organism.

**HUMIC ACID**

Alkali soluble organic matter of soils, may be derived from lignin and may contain nitrogen.

**HUMIN**

The dark amorphous substance formed by the reaction of tryptophane with an aldehyde group, during the acid hydrolysis of a protein.

**HUMOR, AQUEOUS**

See Eye, Biochemistry of.

**HUMOR, VITREOUS**

See Eye, Biochemistry of.

**HUMULENE**

A sesquiterpene of oil of hops.

**HUNTER REACTIONS FOR IMIDAZOLE-ACRYLIC ACID (UROCANIC ACID)**

I. The addition of silver nitrate solution to a solution of the acid, neutralized with ammonia, yields

a precipitate which is soluble in excess ammonia.

II. An alkaline solution of the acid forms a red color with diazobenzenesulfonic acid.

III. The acid reduces alkaline potassium permanganate solution at room temperature.

Reference: J. Biol. Chem. 8, 449 (1910); 11, 537.

## HUNTER HEACTIONS FOR THYMINE

Thymine and diazotized sulfanilic acid in sodium carbonate solution are mixed and, after a short time, treated with sodium hydroxide and hydroxylamine solution, producing an intense red color.

Reference: Biochem. J. 30, 745 (1936).

## HUNTER TEST FOR ERGOTHIONEINE

Reagents—(1) 1.5 cc. 5% sodium nitrate solution are added to 1.5 cc. of a solution of 9 gm. sulfanilic acid and 90 cc. concentrated hydrochloric acid per liter. After standing 5 minutes, 6 cc. more of sodium nitrite are added and after 5 more minutes diluted to 50 cc. (2) 1 gm. anhydrous sodium carbonate and 10 gm. sodium acetate are dissolved in 100 cc. water. 1 cc. (1) and 0.5 cc. (2) are mixed and, after 15 seconds, the test solution is added. Chill for  $\frac{1}{2}$  minute, add 2 cc. 10% sodium hydroxide and shake; a purplish-red color is obtained.

Reference: Biochem. J. 22, 4 (1928).

## HYALURONIC ACID

See Enzymes, Non-Proteolytic.

## HYALURONIDASE

An enzyme of certain streptococcus, pneumococcus and other cultures which destroys the capsules of the organisms.

See Enzymes, Non-Proteolytic.

## HYDANTOIC ACID

See Creatine and Creatinine Metabolism.

## HYDANTOIN

Glycolylurea, m.p. 220°.

See Creatine and Creatinine Metabolism.

## HYDNOCARPIC ACID

$C_{16}H_{28}O_2$ ; a cyclic fatty acid found in Chaulmoogra oil which is used in the treatment of leprosy; crystallizes as leaflets from alcohol; m.p. 59-60°C.

## HYDRASTINE

Levorotatory alkaloid from Hydrastis canadensis; slows heart beat and raises blood pressure; used to contract uterus and quench hemorrhage.

## HYDRASTININE

$C_{11}H_{13}O_3N$ ; needles, m.p. 116-117°; alkaloid of hydrastis Canadensis; in the eye causes dilation of the pupil; internally large doses cause paralysis of the nervous system; in smaller doses is used to prevent parturitional hemorrhages.

## HYDRASTIS

Dried rhizome and roots of Hydrastis canadensis (Golden Seal), containing the alkaloids hydrastine, berberine and canadine; used to check sweating, as tonic and as promoter of uterine contraction.

## HYDRATION

A special case of solvation, where water is the solvent.

## HYDROCHLORIC ACID IN GASTRIC JUICE, TEST FOR

See Günzburg.

## HYDRAERGOTOCIN

See Yohimbine.

**HYDROGEN BOND**

See Protoplasm.

**HYDROGEN ELECTRODE**

A metallic electrode which has been coated with a thin layer of platinum black, and exposed to an atmosphere of hydrogen long enough for the platinum black to become saturated with hydrogen. It behaves as though it were an electrode made of hydrogen, and is used for conveniently and accurately measuring hydrogen ion concentration.

**HYDROGEN LYASE  
(BACTERIAL)**

An enzyme liberating molecular hydrogen from sugars or formic acid.

**HYDROGEN PEROXIDE  
TESTS**

See Arnold-Mentzel.

**HYDROLYSIS**

The addition of water to a compound causing it to split into two parts, one part chemically reacting with the H of the water and the other part with OH.

**HYDROLYTIC ENZYMES**

See Enzymes, Non-Proteolytic

**HYDRONIUM**

A combination of hydrogen ion,  $H^+$ , with a water molecule, giving  $H_3O^+$ . Also OXONIUM ion.

**HYDROXY ACID TEST**

See Liberali.

**HYDROXYAPATITE**

See Teeth, Biochemistry of.

**$\beta$ -HYDROXYBUTYRATE  
ENZYME**

The pyridinoprotein enzyme which catalyzes the equilibrium between the l(-)-form and acetoacetic acid.

**$\beta$ -HYDROXYBUTYRIC ACID**

$C_4H_8O_3$ ; a saturated monohydroxy fatty acid resulting from animal metabolism; m.p.  $42.5^\circ C$ .

**$\beta$ -HYDROXYBUTYRIC  
ACID TEST**

See Hart, Minkowski, Shafer.

**dl-ALPHA-HYDROXY-  
GAMMA-METHIOBUTYRIC  
ACID**

The hydroxy analogue of methionine, excreted as extra cystine in a cystinuric; supports growth on sulfur-deficient diet.

**HYDROXYDEGUELIN**

See Tephrosin.

**$\beta$ -HYDROXYGLUTAMIC ACID**

$C_5H_9O_5N$ ; an amino acid which according to the criteria of Vickery and Schmidt (1931) is not accepted as a proven protein constituent.

**$\alpha$ -HYDROXYGLUTARIC  
HYDROGENASE (HEART)**

An enzyme which catalyzes the oxidation of l(-)-alpha-hydroxyglutaric acid to the corresponding keto compound with pyocyanine as carrier; found in brain, kidney, diaphragm and heart muscles.

**HYDROXYL COMPOUND  
TEST**

See Tschugaev.

**p-HYDROXYPHENYL-  
PYRUVIC ACID**

$C_8H_7OH \cdot CH_2 \cdot CO \cdot COOH$ ; an intermediate of tyrosine metabolism. See also Tyrosinosis. Partly reduced to proline (which see). As hydroxyproline is ketogenic it appears that not all of it follows the same path as proline.

**l-HYDROXYPROLINE  
(OXYPROLINE)**

$C_5H_7O_3N$ ;  $\gamma$ -hydroxy- $\alpha$ -pyrrolidine carboxylic acid; m.p.  $270^\circ$ ;

an amino acid found in many cereal proteins and gelatin.

# **HYDROXY STILBENE DERIVATIVES**

See Estrogens, Synthetic.

# **HYGRINE**

$C_8H_{15}ON$ ; 1-(i-N-methylpyrrolidine)propenone-2; alkaloid of Erythroxylin Coca; alkaline liquid, b.p. 193-195°.

# **HYODESOXYCHOLIC ACID**

$C_{24}H_{40}O_4$ , m.p. 197°; a bile acid found in the hog and the hippotamus; it is 3,6-dihydroxycholanolic acid.

# **1-HYOSCINE**

$C_{17}H_{21}O_4N$ ; a syrupy alkaloid of solanaceous plants. The dl form crystallizes as prisms with  $H_2O$ , m.p. 193-4°, has a more transient action than atropine on the autonomic nervous system. It acts as a depressant on the central nervous system, causing fatigue and sleep.

# **HYOSCYAMINE**

$C_{17}H_{23}O_3N$ ; long silky needles from dilute alcohol, m.p. 108.5°; a commonly occurring alkaloid of solanaceous plants; the l-variety of atropine.

# **HYOSCYAMINE BASE TEST**

See Gerrard.

# **HYOSCYAMUS**

Henbane; dried leaves and tops of *Hyoscyamus niger*, containing the alkaloids hyoscyamine and hyoscine.

# **HYPAPHORINE**

The betaine of tryptophane.

# **HYPERACIDITY**

See Hyperchlorhydria.

# **HYPERADRENOCORTICISM**

See Glycosurias, Non-Diabetic.

# **HYPERALGESIA**

See Itching.

# **HYPERCHLORHYDRIA**

Hyperacidity; abnormal amounts of free HCl secreted by the stomach, a sign of ulcers, gall bladder disease, appendicitis.

# **HYPERGLYCEMIA**

The increased concentration of blood sugar above normal for any reason, such as diabetes.

# **HYPERGLYCEMIA, EMOTIONAL**

See Psychiatry, Biochemistry of.

# **HYPERGLYCEMIC INDEX**

An estimate of rate of glucose assimilation by tissues, as the percentage obtained in dividing 2 hour level minus fasting level of blood sugar by the maximum level minus the fasting level; is zero for normal persons.

# **HYPERINSULINISM**

See also Hypoglycemia, Insulin.

# **HYPERMENORRHEA**

Menorrhagia (old term); excess of menstrual flow.

# **HYPERPIESIA**

Essential hypertension; a prolonged rise in arterial pressure greater than 160 systolic or 90 diastolic without anatomic causative factor in the kidney or blood vessels, said to be familial and attributed to nervous tension. Reduction of pressure is to suit the patient's comfort rather than a therapeutic measure. Complications are often arteriosclerosis, cardiac failure, coronary thrombosis, uremia. Vasodilators (nitrites and theobromine) are used to alleviate symptoms. Cautious use of iodides, thiocyanates and hormones is advised. The most rational advice on diets restricts

intake of fluids but little else outside of overeating. Psychotherapy is important.

# **HYPERPITUITARISM**

See also Glycosurias, Non-Diabetic.

# **HYPERTENSION, ESSENTIAL**

See Hyperpiesia.

# **HYPERTENSION, RENAL**

See Oxyrenin.

# **HYPERTHYROIDISM (EXOPHTHALMIC GOITRE)**

A constitutional disease involving excess secretion from a diffusely hypertrophied thyroid, causing any increased metabolism.

See Goiter; Glycosurias, Non-Diabetic.

# **HYPERTONIC**

A concentration of solution greater than the cell or system to which it is compared.

# **HYPERTROPHY**

See Autolysis.

# **HYPOGAEIC ACID**

A 16 carbon homologue of oleic acid, found in peanut and maize oils, m.p. 33°.

# **HYPOGLYCEMIA**

A condition of abnormally low sugar in the blood, i.e. below 80 mg. per cent. It may include hyperinsulinism and insulin shock because of the definition as a symptom and not a disease. Thus, too, liver disease and any failure in the supply of hormones, e.g. epinephrine, which inhibit insulin will bring about hypoglycemia. Addison's disease would do so by destruction of the adrenals. Pituitary destruction (Simmonds' disease) would operate by the loss of the antagonistic diabetogenic hormone. Thy-

roidectomy has a similar effect. Feeding carbohydrates or the missing hormone epinephrine are obvious emergency procedures. If the hyperinsulinism is due to malignant disease of the pancreas surgery is required.

# **HYPOMENORRHEA**

Abnormal decrease of menstrual flow. Etiology same as for Amenorrhea (which see).

# **HYPOMETABOLISM**

A depression of the basic metabolic rate in conditions of undernutrition, sleep, thyroidectomy, etc.

# **$\alpha$ -HYPOPHAMINE**

Oxytocin.

# **$\beta$ -HYPOPHAMINE**

Vasopressin.

# **HYPOPHYSIS**

The pituitary gland. A number of extremely important hormones are produced in its four parts.

# **HYP-O-VARIANISM**

Hypogonadism in the female; deficiency of ovarian function which grades to cessation of ovarian function, or menopause, with its accompanying symptoms of nervous disturbance and amenorrhea. It may be primary when it is due to delayed or retarded development, eunochoidism or infantilism, or is due to pathological or surgical loss, or due to vitamin deficiency. Pituitary dysfunction is a more remote cause making the hypo-ovarianism secondary. Menopause may be natural (between the 40th and 50th years), premature (due to disease) or artificial (due to castration). Hypo-ovarianism shows in menstrual disturbances as amenorrhea (cessation of flow),



oligomenorrhea (irregularity of flow), menorrhagia (hypermenorrhagia), or metrorrhagia (polymenorrhagia); eunuchism; poor development or regression of secondary sex characteristics. Nervous symptoms include "the blues," decreased memory, and insomnia. Cardiovascular symptoms are "hot flushes," palpitation and dizziness. Other symptoms attach themselves to these readily. The symptoms are even more marked in menopause. The treatment is causal and leads to substitution of estrogenic hormones to make up for their decreases. Estriol, estrone or estradiol and their derivatives may be used.

#### HYPOSTHENURIA

Inability to perform normal concentration of the urine.

#### HYPOTHYROIDISM

A deficiency of the thyroid hormone which is shown by a decrease of basal metabolic rate. It takes on the forms of (1) cretinism (2) infantile myxedema (3) adult myxedema and (4) hypothyroidism without myxedema. The first two forms have an intra-uterine origin, leading if unchecked to dwarfism and idiocy. Myxedema of adults comes gradually. Besides low basal

metabolism there is hypercholesterolemia, lowered tolerance for dextrose and diminished sensitivity to epinephrine and pilocarpine. In forms in which myxedema is absent response to thyroid medication is good. There is a general "neurasthenic syndrome" consisting of insomnia, lack of appetite (anorexia), fatigability and vague pains.

#### HYPOTONIC

(1) Marked by abnormally low tension. (2) Less than isotonic: said of solutions which are of less than isotonic concentration.

#### HYPOVITAMINOSIS B<sub>1</sub>

See Beriberi.

#### HYPOXANTHINE

6-oxypurine, a breakdown product of nucleoproteins via adenine and the action of adenase.

#### HYPOXANTHINE RIBOSIDE

See Inosine.

#### HYPOXANTHINE TEST

See Kossel.

#### HYPOXANTHOSIN

See Inosine.

#### HYSTERESIS

The dependence of the state of a physical system not only upon environmental parameters, but upon the sequence of states through which it has previously passed.

# I

## ICHTHULIN

An old name for the compound in fish eggs corresponding to ovotellin of hen's eggs.

## ICTERIC INDEX

A ratio used as a test for bilirubin and jaundice. Diluted blood serum is treated with acetone, filtered and compared with 1:10000 potassium dichromate. The ratio of the standard to the unknown, times the dilution is the icteric index, normally 4 to 6.

## ICTERUS

See Jaundice.

## IDAEIN

Cyanidin-monogalactoside; an anthocyanin of the cowberry (mountain canberry); forms a chloride,  $C_{21}H_{21}O_{11}Cl \cdot 2\frac{1}{2}H_2O$ ; melting at  $120^\circ$ .

## ILETIN

A commercial insulin preparation.

## ILEUM

See Gastro-Enterology.

## IMBECILLITIS

## PHENYLPYRUVICA

Phenylketonuria.

## IMBIBITION

See Protoplasm.

## IMBIBITION PRESSURE

The pressure against which a lyophilic colloid will imbibe a liquid, or conversely, that pressure which will be needed to

force the dispersions medium out of a gel, or similar colloid.

## IMIDAZOLES, TESTS FOR

See Koessler-Hanke, Pauly.

## IMMUNE- POLYSACCHARIDES

Five types of polysaccharides which usually contain uronic acids and may contain some nitrogen; isolated from bacteria and involved in the production of immunity.

## IMMUNE SERA

See Immunological Phenomena.

## IMMUNOLOGICAL PHENOMENA<sup>1</sup>

Substances inciting the formation of and reacting with antibodies are named antigens. Sera that contain antibodies as the result of the injection of antigens<sup>2</sup> are called "immune sera" or "antisera," while the designation "normal" or "natural" antibodies is applied to substances found in the sera of untreated animals, which are similar in their effects to the antibodies developed by immunization. A rather detailed nomenclature has been built up around the diverse manifestations of antigen-antibody reactions, the antigens and antibodies being described with reference to the kind of reaction observed; but it is necessary to state at the outset that the same antibodies can act in various capacities, e.g., as agglutinins and precipitins.

Poisonous antigens characterized by high toxicity and their capacity of being fully neutralized, even in high multiples of the lethal dose, by their antibodies are termed toxins or exotoxins (as the toxin of the diphtheria bacillus). This name includes substances which destroy cells, e.g., the hemotoxin (or hemolysin) of tetanus bacilli, the leucocidin of staphylococci, etc.; the neutralizing antibody is called antitoxin. Toxoids are an atoxic modification of toxins which retain binding power and antigenicity. The clumping of cells is known as agglutination, and the antigens and antibodies involved are called agglutinogens and agglutinins (hemagglutinins, bacterial agglutinins) respectively. Similarly, the antibodies causing disruption of cells (lysis) are designated as lysins (bacteriolysins, hemolysins), precipitins those which cause precipitation when mixed with the inciting soluble antigens (precipitinogens), while tropins (opsonins) are antibodies that render cells susceptible to ingestion by leucocytes (phagocytosis).

Referring to the ability of antigens to induce a state of sensitivity and subsequently to produce the symptom-complex known as anaphylaxis the term anaphylactogen is in use. The anaphylactic state is induced by parenteral administration of a protein: to describe a typical experiment, after 0.01 cc. of ox serum has been injected into a guinea pig (and much smaller doses may be effective, as 0.0001 cc. or less), and an interval of 10 days or longer has elapsed, a second (intravenous) injection of, say, 0.1 cc. kills the animal in a few minutes under characteristic and violent symptoms (choking, convulsions,

dyspnoea); or, a rabbit previously sensitized would show intense local inflammatory and necrotic reactions on subcutaneous reinjection of the same antigen (Arthus phenomenon). The anaphylactic condition can be transferred with the serum of sensitized animals to normal ones (passive anaphylaxis) and, fundamentally, the phenomenon has the significance of an antigen-antibody reaction in vivo and can be used in place of a reaction in vitro. The opinion that these reactions generally exhibit greater specificity than in vitro tests, would require confirmation. The designation allergen connotes the ability of certain materials to induce specific allergic manifestations, denoted by Coca as atopic diseases (hay fever, asthma), and the associated special antibodies in the serum of such patients are known as reagins a name also given to some other agents (Wassermann reagins).

Antibodies produced with material taken from the animal selected for immunization, or from other individuals of the same species, are referred to as auto- or isoantibodies respectively. The expression passive immunization, in contrast to active immunization, signifies the (temporary) protection conferred upon an animal by the administration of immune sera. Reactions of an antibody with its corresponding antigen are said to be homologous, while heterologous reactions, known also as overlapping, cross or group reactions, are those taking place with (related) substances other than the inciting antigen.

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<sup>1</sup> From Landsteiner's "The Specificity of Serological Reactions," 2nd Ed. Cour-

tesy of Charles C. Thomas, Publisher, Springfield, Ill.

<sup>2</sup> In amplification of its original meaning the term immunization is commonly used also when antigens are not harmful and the antibodies which are formed have no curative or protective role.

# IMPULSE, MUSCLE

See Bioelectric Potentials.

# IMPULSE, NERVE

See Bioelectric Potentials.

# INCARNATRIN

See Flavonol Glycosides.

# INDENE-3-ACETIC ACID

Plant Growth Hormones.

# INDIAN HEMP

*Cannabis Indica*; dried flowering tops of *Cannabis sativa* (hashish), a narcotic; habit forming.

# INDICAN

$C_{14}H_{17}O_6N \cdot 3H_2O$

1—A glycoside of Indigofera, consisting of glucose and indoxyl; brown rhombic crystals, m.p. 50°.

2— $C_6H_5NH \cdot CHCOSO_2OK$ , potassium indoxyl sulfate, arising in animals from bacterial decomposition of tryptophane in the intestines.

# INDICAN TESTS, IN URINE

See Bouman, Ehrlich, Fischer-Huppmann, Gruber.

# INDICATOR

A substance, which when added in small amounts to a chemical system, shows, by an easily discernible change of color or some other characteristic, a condition of the system or reaction; i.e. pH, etc.

# INDICATOR YELLOW

See Visual Yellow.

# INDIGO

The dyestuff of the glycoside, indican, found in indigo where it exists in a reduced form.

# INDIVIDUATION

The field system of headness and tailness of developing cells.

# INDOLE

$CH:CHC_6H_4NH$  m.p. 52.5°; cyclic amine resulting from bacterial decomposition of tryptophane; partly responsible for the odor of feces and decaying protein; present in urine as indican. In large amounts it produces stupor and weak heart action.

# INDOLE-3-ACETIC ACID

Plant Growth Hormones.

# INDOLEACETIC ACID TESTS

See Herter, Salkowski.

# INDOLEPYRUVIC ACID

A compound supposed to be an intermediate in tryptophane metabolism.

# INDOLE TESTS

See Denigès, Hopkins, Kovacs, Legal, Montignie, Zappacosta.

# INDOPHENOL OXIDASE

A component, with cytochrome, of the oxidation system of the cell; gives a blue color with paraphenylenediamine and alpha naphthol.

# INDOPHENOL TEST

A test for the presence of oxidizing enzymes in cells and for detecting the presence of myeloblasts, etc.

# INDOXYL

$C_8H_7ON$ , m.p. 85°, excreted as a sulfate in urine as a decomposition product of tryptophane; also occurs naturally as a component of indican.

# INDOXYL TEST (IN URINE)

See Maillard.

# INDUCTOPYREXIA

See Fever Therapy.

# INFANTILE PARALYSIS

See Poliomyelitis.

**INFECTIOUS AGENTS,  
INHIBITION OF GROWTH**

See Chemotherapy.

**INFUSORIA**

See Protozoa.

**INHIBITOLS**

An occasional equivalent term for antioxidants or antioxygens.

**INJURY POTENTIAL (Current)**

See Potentials, Bioelectric.

**INOSINE**

A nucleoside consisting of hypoxanthine and d-ribose, formed by deamination of adenosine; forms inosine phosphoric acid; hypoxanthosine; hypoxanthine riboside.

**INOSINIC ACID**

A mononucleotide consisting of one molecule of hypoxanthine, d-ribose, and phosphoric acid.

**INOSITOL**

Hexahydroxyhexahydrobenzene, occurring very widely in seeds.

**d-INOSITOL**

m.p. 247° positive rotation.

**l-INOSITOL**

As above, negative rotation.

**i-INOSITOL**

Dambose; nucite; m.p. 225°.

**INOSITOL TESTS**

See Perrin, Salkowski.

**INOUE TEST FOR BLOOD**

10 cc. of test liquid are treated with 10 cc. alcohol and 5 cc. chloroform and shaken lightly; 10-20 drops each of a freshly prepared guaiac tincture and of ozonized turpentine oil are then added. A temporary blue-violet color is obtained in the chloroform layer.

Reference: Arch. Verdauungs-Krankh. 18, 223 (1912).

**INSECT PUPATION**

See Autolysis.

**INSULIN**

Insulin, the internal secretion of the pancreas, is formed in the islet

tissue of that organ and passes from there into the general circulation. Its presence is indispensable for the normal maintenance of carbohydrate metabolism in mammals. In cases of pronounced hypofunction the typical symptom complex of diabetes mellitus is observed. With excessive production of the hormone a physiological state ensues which is conveniently designated as hyperinsulinism.

Banting and Best<sup>1</sup> succeeded in 1922 in obtaining from the pancreas potent hypoglycemic extracts, suitable for clinical use in the treatment of diabetes mellitus. It is beyond the scope of this article to discuss the huge volume of the preceding work in this field; for further information the reader is referred to the following references, (B, C, D, G).

Isolation and Chemistry: Following the successful achievement of obtaining potent extracts of the hormone from the pancreas, numerous efforts were undertaken to isolate the active principle as a crystalline chemical entity, (B, C, D, G).

Insulin was first obtained in crystalline form by Abel and his associates in 1926 from highly purified commercial preparations.<sup>2</sup> The method of Abel and his collaborators in obtaining crystalline preparations consists of the isoelectric precipitation of the hormone from a strongly buffered acetic acid solution by the addition of a weak base. The pH of the final solution was found to be about 5.6. Modified procedures of obtaining crystalline insulin preparations have been worked out by several investigators, (A, B, C, D, G). Although crystalline insulin is usually prepared from beeves' pancreas, it can also be obtained from the islet tissue of

certain fishes<sup>3, 4</sup> and from pig<sup>4</sup> and sheep<sup>4</sup> pancreas. Insulin crystals were found to possess a physiological activity of 24 international units per milligram (see Standardization).

The accumulated results of the chemical investigations on crystalline insulin reveal that this hormone must be classified as a typical protein. Its complex protein-like nature affords little hope at present, for the elucidation of its exact structure and for its synthesis. The pharmacodynamic functions of the hormone are apparently connected in some way with the manner in which the component amino acids are linked, since analytical work has so far

failed to disclose any especial constituent or property, which would explain the unique action of this principle in the animal body. The chemical behavior of insulin towards certain reagents seems to indicate that the physiological properties of insulin are associated with certain groupings in the molecule, e.g., the dithio (-S-S-) linkages (present as cystine), with the hydroxyl groups (tyrosine) and also apparently with a part of the free amino groups, (A, B, C, D, E, F, G,H).

The following amino acids have been found to be present in the insulin molecule.

Table I  
Amino Acids in Insulin

Amino Acids	Per cent	Method of Determination
Tyrosine	12	Colorimetrically
Cystine	12	Colorimetrically
Arginine	3	Colorimetrically and calculated from Van Slyke nitrogen distribution
Histidine	4	Colorimetrically and calculated from Van Slyke nitrogen distribution
Lysine	2	Calculated from Van Slyke nitrogen distribution
Proline	10	Calculated from nonamino nitrogen of Van Slyke nitrogen distribution
Glutamic acid	20	Calculated from amide nitrogen of Van Slyke nitrogen distribution
Phenylalanine		Isolated as phenyl-hydantoin
Leucine		Isolated as such

No reliable methods for the quantitative determination of leucine and phenylalanine are as yet available. Hydroxyproline has been found to be absent.<sup>5</sup> It seems therefore that all the nonamino nitrogen as found in the Van Slyke nitrogen distribution is present in the form of pro-

line. Aspartic acid does not seem to be present. In addition to the amino acids isolated, evidence for the presence of isoleucine and of valine<sup>5</sup> and of hydroxy amino acids, probably serine,<sup>6</sup> has been obtained. In spite of various attempts, no evidence has thus far been obtained for



the occurrence in the insulin molecules of any constituent differing in its structure from the known amino acids protein components. The high sulfur content (3.3 per cent) of insulin has been of particular interest. It has now been established that all the sulfur can be accounted for as cystine.<sup>7</sup>

**Standardization:** The evaluation of the potency of an unknown insulin preparation is made by comparing its hypoglycemic action with that of the international standard powder under carefully controlled conditions. The international unit which is now accepted is the activity contained in 0.125 mgm. of the international standard preparation. The activity of various commercial insulin preparations and of crystalline insulin is expressed in terms of this international standard.

Two procedures have been devised to determine the activity of insulin preparations by comparison with the standard and are now generally employed: (a) method dependent upon the production of convulsions, and (b) method based upon the determination of the decrease in blood sugar.

Briefly stated, method (a), which usually employs mice as test animals, is based upon the comparison of the percentage of convulsions produced in white mice kept at 38°, half of the mice being injected intraperitoneally with the standard preparation and the other half with the solution of unknown unitage. The mouse dose is defined as the quantity producing convulsions in one-half the number of mice injected.

Method (b) of assaying insulin has gained wide acceptance. Rabbits are generally used in this pro-

cedure which consists of injecting subcutaneously a suitable dose of the standard insulin preparation into one-half of a series of rabbits of 2 kilo weight and previously starved for eighteen to twenty-four hours, the other half simultaneously receiving a dose of the sample of unknown unitage. Several days later the groups are crossed over and used for the injection of the same preparations. Blood samples are usually taken at one and one-half, at three, and at five hour intervals after the injections. From the relation between the blood sugar lowering produced by the standard insulin and by the insulin of unknown potency, the activity of the latter can be calculated. A few general references on the standardization of insulin are included in the bibliography (B, C, D, 8, 9).

**Administration:** Insulin is administered to diabetic patients at present mainly by the subcutaneous route and sometimes in cases of emergency, by intravenous injection. There are associated with these generally accepted methods of administration, certain practical difficulties which investigators have for many years recognized and attempted to remedy. Chief among these difficulties are: (1) the discomfort accompanying injection, and, (2) the unavoidable frequency of dosage with its attendant disadvantages.

Oral administration of the hormone obviously would be the most convenient. However, since insulin activity is destroyed by proteolytic enzymes, no attempt to give the hormone by mouth can succeed unless practical measures for its protection against the action of trypsin or pepsin be perfected. In spite of various attempts, there is, unfortu-

nately, at present no preparation of insulin available which can be given by mouth and which can be relied on to take the place of the insulin preparations which must now be given by injection.

Other experiments were carried out with the object of combining or mixing insulin with substances in order to decrease its rate of absorption from the tissue. Such delayed absorption would permit the use of larger doses and thus reduce the number of daily injections required. Hagedorn and his associates<sup>10</sup> were the first to produce an insulin preparation possessing prolonged blood sugar lowering action and suitable for therapeutic use. These investigators demonstrated that when a solution of protamine in sodium phosphate buffer is added to an insulin solution, an insulin protamine complex is formed at pH 7.2. On subcutaneous injection of a suspension of this complex, prolonged hypoglycemia is produced. These investigators also reported successful results from the administration of protamine-insulin to diabetic patients. The importance of this finding was immediately recognized and was followed by further attempts of different investigators to obtain even more useful insulin preparations.

Shortly after Hagedorn's finding, Scott and Fisher<sup>11</sup> reported that the addition of zinc to insulin prior to the addition of protamine, prolonged still further the hypoglycemic effect of the hormone. The superiority of protamine-zinc-insulin to unmodified protamine-insulin and to "regular" insulin has been substantiated by numerous clinical tests. Protamine-zinc-insulin and "regular" insulin are at present used clinically.

Various combinations of insulin with other basic compounds in the presence of certain heavy metal ions have been prepared and found to produce prolonged hypoglycemia. However as yet no preparation has been obtained which could be considered to be clinically superior to protamine-zinc-insulin.

**Substitutes:** The clinical use of the various commercial insulin preparations for the relief of the symptoms of diabetes mellitus can be considered an entirely satisfactory and successful therapeutic measure. The fact that insulin is ineffective when administered orally has led to efforts to obtain nontoxic insulin substitutes which are active when given by mouth. At present, however, no substance fulfilling these requirements has been prepared.

The possibility of the existence of insulin-like substances in plants has been investigated at various times. Although different plant extracts have been prepared which, it was claimed, exerted a hypoglycemic effect, little has been done, either in substantiation or extension of these investigations. In many instances substances obtained from plant sources and possessing hypoglycemic action were found to be rather toxic, and have accordingly not found to be useful in medical practice, (B, C, D, G).

Frank and his associates<sup>12</sup> have studied the effect of various polymethylenediguanidines on the blood sugar. Synthalin, (decamethylenediguanidine), and neosynthalin, (dodecamethylenediguanidine), were found to be the most active of the different diguanidino derivatives studied by them. Both compounds were used for a short time in the treatment of certain diabetic

cases. Because of the toxic effects of these substances their clinical use has been discontinued.

**Physiological Action:** The chief role of insulin is concerned with the regulation of important phases of metabolism. Metabolism is generally defined as the sum total of the chemical changes which occur in the various tissues of the body. Metabolism is controlled by the proper physiological coordination of various active agents in the body; as such agents we may classify enzymes, vitamins and hormones. The efficiency with which the regulatory mechanisms of the endocrine system on metabolism counteract each other, depends to a large extent on its normal balance. Any relative or absolute deficiency or preponderance of certain endocrine secretions may result in a definite abnormal shift of general metabolism. The exact role which each of the different endocrine principles plays in the process of metabolism, has not yet been fully established. The liver is in all probability the organ through which the influence of the endocrine system on metabolism is mainly exerted. The influence of certain endocrines on metabolism manifests itself by observing the main alterations in metabolism which occur in the absence of these endocrine organs.

The importance of insulin with regard to metabolism becomes evident upon examination of the physiological disturbances in the body which one observes in the absence of the secretion of insulin (pancreatectomy, diabetes mellitus). The following symptoms have been found to be characteristic:

(1) Pronounced hyperglycemia and glycosuria.

(2) Depletion of the glycogen stores in certain tissues (liver, muscle).

(3) Lowering of the respiratory quotient indicating incomplete combustion of glucose.

(4) Increase in the glucose-nitrogen ratio in the urine probably due to an increase in the conversion of protein into glucose.

(5) Development of acidosis probably caused by imperfect fat metabolism.

Injection of insulin will relieve all these symptoms and reestablish a practically normal metabolism. Administration of insulin also affects specifically the carbohydrate metabolism of the normal organism.

The following functions may be attributed to insulin:

(1) Acceleration of glucose oxidation in the tissues.

(2) Increase in the rate at which glucose is converted to glycogen in the muscle and in other tissues. It is still unsettled whether insulin has a direct influence on the formation of liver glycogen or whether it inhibits hepatic glycogenolysis which is caused by certain other hormones. This inhibitory effect of insulin would enable the liver of the normal animal to retain its glycogen, and would also account for the disappearance of liver glycogen in the depancreatized animal (absence of insulin).

Increase in glucose oxidation and in the rate of glycogen formation probably accounts for the fall in blood sugar observed after insulin injection.

(3) Inhibition of carbohydrate formation in the liver from non-

carbohydrate sources. Gluconeogenesis is apparently under the control of certain other endocrine principles.

(4) Prevention of the formation of ketone bodies which are formed as a result of deranged fat metabolism.

Decrease in glucose oxidation and increase in hepatic glycogenolysis and gluconeogenesis suggests that hyperglycemia may be due to the following factors:

(a) Deficient supply of insulin.

(b) Liberation, either at a normal or excessive rate, of those principles which play a role in glycogenolysis and in gluconeogenesis.

It should be reemphasized that in any study of the physiological action of a hormone, its relationship to various other endocrine principles and also to such active agents as vitamins and enzymes has to be taken into consideration. For further information on the physiological action of insulin the reader is referred to the following references, (B, C, D, G, K, 13 to 19).

\*Footnote

No attempt has been made to give a complete bibliography. For further information on the different aspects of insulin the reader is referred to the general references A to K.

H. JENSEN

The Upjohn Company  
Kalamazoo, Mich.

A. Jensen, H. and Evans, Jr., E. A.: *Physiol. Rev.* 14: 188 (1934).

B. Hill, D. and Howitt, F.: *Insulin, Its Production, Purification and Physiological Action*, Hutchinson's Scientific and Technical Publications, London 1936.

C. Geiling, E. M. K., Jensen, H. and

Farrar, Jr., G. E.: *Insulin, Handbuch der Experimentellen Pharmakologie, Ergaenzungswerk*, vol. V., 197, (1937).

D. Jensen, H.: *Insulin, Its Chemistry and Physiology*, The Commonwealth Fund, New York 1938.

E. Du Vigneaud, V.: *Cold Spring Harbor Symposia on Quantitative Biology*, vol. 6, 275, (1938).

F. White, A.: *Cold Spring Harbor Symposia on Quantitative Biology*, vol. 6, 262, (1938).

G. Houssay, B. A. and Deulofeu, V.: *La Chimie et la Sécrétion de l'Insuline; Ergebnisse der Vitamin- und Hormonforschung*, vol. 2, 297, (1939).

H. Annual Review of Biochemistry, Stanford University, California.

K. Annual Review of Physiology, Stanford University, California.

BIBLIOGRAPHY

<sup>1</sup> Banting, F. G. and Best, C. H.: *J. Lab. & Clin. Med.* 7: 464 (1921-22).

<sup>2</sup> Abel, J. J., Geiling, E. M. K., Rouiller, C. A., Bell, F. K. and Wintersteiner, O.: *J. Pharmacol. & Exper. Therap.* 31: 65 (1927).

<sup>3</sup> Jensen, H., Wintersteiner, O. and Geiling, E. M. K.: *J. Pharmacol. & Exper. Therap.* 32: 287 (1928).

<sup>4</sup> Scott, D. A.: *J. Biol. Chem.* 92: 281 (1931).

<sup>5</sup> Jensen, H. and Casey, J. J.: *Unpublished Results*.

<sup>6</sup> Nicolet, B. H. and Shinn, L. A.: *J. Am. Chem. Soc.* 63: 1486 (1941).

<sup>7</sup> Du Vigneaud, V., Miller, G. L. and Rodden, C. J.: *J. Biol. Chem.* 131: 631 (1939).

<sup>8</sup> Quarterly Bulletin of the Health Organization of the League of Nations, vol. 4, 525, 641, Geneva (1935).

<sup>9</sup> Burn, J. H.: *Biological Standardization*, Oxford Medical Publications, London, (1937).

<sup>10</sup> Hagedorn, H. C., Jensen, B. N., Krarup, N. B., and Wodstrup: *J. Am. Med. A.* 106: 177 (1936).

<sup>11</sup> Scott, D. A. and Fisher, A. M.: *J.*

Pharmacol. & Exper. Therap. 58: 78 (1936).

<sup>12</sup> Frank, E., Nothmann, M. and Wagner, A.: Klin. Wchnschr. 7: 1996 (1928).

<sup>13</sup> Drury, D. R.: J. Clin. Endocrinology 2: 421 (1942).

<sup>14</sup> Chambers, W. H.: Physiol. Rev. 18: 248 (1938).

<sup>15</sup> Russell, J. A.: Physiol. Rev. 18: 1, (1938).

<sup>16</sup> Long, C. N. H.: Transactions and Studies of the College of Physicians of Philadelphia, 4 Ser., vol. 7, 21 (1939).

<sup>17</sup> Carbohydrate Metabolism, Endocrinology 26: 285-345 (1940).

<sup>18</sup> Haist, R. E., Campbell, J. and Best, C. H.: New England Journal of Medicine 223: 607 (1940).

<sup>19</sup> Soskin, S.: Northwest Medicine, Seattle, Oct. Nov. Dec. (1941).

## INSULIN IN MENTAL DISEASE

See Psychiatry, Biochemistry of.

## INSULIN, PROTAMINE-ZINC

See Protamine-Zinc-Insulin.

## INSULIN TEST

See Wyss.

## INSULIN UNITS

The international unit is the activity of 0.125 mg. of a standard preparation of dry insulin hydrochloride. One mg. of this international standard contains 22 units as defined by the Insulin Committee of the University of Toronto, their unit being the amount needed to produce convulsions in a 2 kg. rabbit in a specified time after injection (20 minutes).

## INTARVIN

Glyceryl margarate, a synthetic fat with an odd number of carbons in the acid, recommended for use in diabetes.

## INTERCOSTAL MUSCLES

See Respiration.

## INTERCOSTAL NERVES

See Respiration.

## INTERMEDIN

A melanophore expanding hormone of the pars intermedia of the pituitary.

## INTERNAL RESPIRATION

See Respiration.

## INTERNAL SECRETIONS

The products of the adrenals, pituitary, pancreas, thyroid, parathyroid, thymus, pineal gland, sex glands.

## INTERNATIONAL ANDROGENIC UNIT

The equivalent of 100 gamma of androsterone.

## INTERNATIONAL PROGESTATIONAL UNIT

The equivalent of 1 milligram of progesterone.

## INTERNATIONAL VITAMIN D UNIT

The equivalent of 0.025 gamma of calciferol.

## INTERRENIN

A commercial preparation of natural adrenal cortex hormone.

## INTERSTITIAL CELLS

Cells of testis or ovary arising from the germinal epithelium and secreting sex hormones.

## INTESTINE

See Gastro-Enterology.

## INTRAOCULAR FLUID

The water-like fluid of the aqueous humor, pH 7.4; closely resembles cerebrospinal fluid; probably formed as a serum dialysate modified by secretions of the ciliary epithelium.

**INTRINSIC FACTOR (CASTLE)**

An anti-anaemic factor obtained from desiccated stomach and duodenal mucosa.

**INULIN**

A white polysaccharide, found in plants, dispersible in hot water. It is hydrolyzed by inulase to fructose.

**INULINASE**

See Enzymes, Non-Proteolytic.

**INVERTASE**

Sucrase.

See Enzymes, Non-Proteolytic.

**INVERT SUGAR**

A mixture of glucose and fructose obtained by acid hydrolysis of sucrose, so named because the optical rotation is inverted from dextro to levo after hydrolysis.

**IODINE ABSORPTION NUMBER**

Iodine number.

**IODINE NUMBER**

The number of grams of halogen, calculated as iodine, which 100 grams of fatty acid or other fatty substance or any unsaturated compound will take up; it is a measure of the degree of unsaturation.

**IODINE NUMBER DETERMINATION**

See Hanus, Hübl, Wijs, Zulkowsky.

**IOLOGORGOIC ACID**

3,5-di-iodotyrosine; an amino acid found in the proteins of many organisms, and in marine thyroids.

**IODOPSIN**

Visual violet; a carotenoid conjugated protein with prosthetic radical which is a vitamin A derivative, found in cones of the retina; plays a similar role to rhodopsin in dark adaptation.

**IODOTHYROGLOBIN**

The iodine containing protein of the thyroid which, at least to a large extent is the hormone of the thyroid. Thyroxine is contained in the molecule. An insufficiency results in goiter, cretinism or myxedema, an excess in an abnormally high metabolism.

**ION ANTAGONISM**

The mutual undoing of effects of various ions, e.g. calcium vs. sodium, magnesium vs. calcium, potassium vs. sodium. This antagonistic action has been followed with respect to surface tension effects, gelling and liquefaction of protoplasm, changes in viscosity and zeta potential.

**IONIZATION CONSTANT**

See Dissociation Constant.

**IONONES**

$C_{13}H_{20}N$ ; isomeric forms made from citral, having the odor of violets.

**IONS**

The electrically charged particles that make up an electrolyte.  
See Ion Transfer (Therapeutic).

**ION TRANSFER (THERAPEUTIC)**

Iontophoresis; the introduction of soluble salts into the tissues by means of direct current. The objective is to deposit ions in or on tissue which may exert varying effects desired, including coagulation of proteins and destruction of tissues. On the other hand drugs may be thus introduced which would have healing effects and conceivably dispersive effects. The potential insures greater effect than topical application. Various electrodes have been devised consisting of a positive metal pole in contact with a fabric saturated with the



solution to be applied. The negative pole is dispersive and is connected to the other side of the patient. The currents are of the order of 5-10 milliamperes and are applied for about 30 minutes at unulcerated places on the skin. Substances which have been applied routinely are 0.2 to 0.5 percent solutions of acetyl-beta-methylcholine chloride (methylol chloride) and 0.1 per cent solution of the acid phosphate of histamine. The conditions treated were those of chronic rheumatoid arthritis.

Reference: Report of Council on Pharmacy and Chemistry and the Council on Physical Therapy, Jour. Amer. Med. Assoc., Vol. 117:5:360 (1941).

i.p.

Isoelectric point.

#### IPECACUANHA

A dried root of *Cephaelis ipecacuanha* (Brazil) containing the alkaloids emetine and cephaeline; expectorant and emetic, used in colds and amoebic dysentery.

#### IPURANOL

A sitosterol-d-glucoside obtained from the stems of *Ipomoea purpurea* and other plants; m.p. 290-295°.

#### IRIDINE

The protamine of the rainbow trout, consists mostly of arginine.

#### IRIDOCYTE

See Guanophore.

#### IRIS

See Eye, Biochemistry of.

#### IRISIN

A fructosan of the rhizomes of the Iris plants.

#### IRON PIGMENTS IN LIVER, TEST FOR

See Guilhon.

#### IRON TESTS

See Andreasch.

#### ISATIN

An oxidation product of indigo; isatinic acid anhydride; o-amino-benzoylformic anhydride; m.p. 198-203°; used as a reagent for cuprous ions, thiophene, mercaptans and indican.

#### ISATROPYLCOCAINE

See Truxilline.

#### ISINGLASS

The inner membrane from the swimming bladder of certain species of sturgeon and hake and consisting chiefly of glutin.

#### ISO ALLOXAZINE

The nucleus found in the flavins.

#### ISOANTIBODIES

See Immunological Phenomena.

#### ISOASCORBIC ACID TEST

See Bachstetz-Cavallini.

#### ISOCITRIC ENZYME

The pyridinoprotein enzyme containing coenzyme II which catalyzes the oxidation of isocitrate to alpha-ketoglutarate; found in heart, kidney, adrenal gland, etc.

#### ISOCONVOLVULIN

See Phorbital.

#### ISOCYTOSINE TEST

See Wheeler-Johnson.

#### ISODULCITE

See Rhamnose.

#### ISOELECTRIC POINT

The hydrogen ion concentration at which the undissociated residue of an amino acid is a maximum, and at which the sum of the ions is minimal. It is that concentration at which there will be a tendency for as many cations to migrate to the cathode, as anions to the anode. In terms of Zwitterions, the i.p. is that H concentration where the ampholyte exists to a maximum as a Zwitterion,

and at a minimum with free acid or basic groups.

**ISOLACTOSE**

See Disaccharides.

**d-ISOLEUCINE**

$C_6H_{13}O_2N$ ;  $\beta$ -methyl,  $\beta$ -ethyl- $\alpha$ -amino propionic acid; plates, m.p.  $280^\circ$ ; an indispensable amino acid found in fibrin and other proteins.

**ISOLYSIS**

See Wound Healing.

**ISOMERASES**

Enzymes which catalyze isomerizations, e.g. 3-phosphoglyceric acid to 2-isomer and phosphopyruvic acid.

**ISOPULEGONE**

A monocyclic ketone found with pulegone in pennyroyal oil.

**ISOPURPURINE**

See Purpurin.

**ISOPYROVITAMIN**

An isomer of calciferol, obtained from it by heat treatment. It contains 4 rings and 3 conjugated double bonds.

**ISOQUININE**

See Pseudoquinine.

**ISOTONIC**

An osmotic pressure of solution equal to that of the cell or system to which it is compared.

**ISOTOPES**

Atoms with the same atomic

number and outer electron system giving similar chemical properties, but differing in nuclear mass.

**ISOTREHALOSE**

See Disaccharides.

**ISOVALERIC ACID**

2-methylbutyric acid; occurs in roots of valerian and angelica.

**ITCHING**

"An unpleasant cutaneous sensation which provokes the desire to scratch" (Haffenreffer). It is intermediate between light tickling and diffuse burning pain. Injury to the skin provokes hyperalgesia, sensitivity to the slightest touch. Spontaneous itches, as in eczema, prurigo, urticaria, are due both to toxic irritation and to stimulation of nerve endings. "Mnemo-dermia" or skin memory is a kind of sensitivity to itching on rubbing a place which had been involved in an itching skin disease previously. Chemical mediation of itching has been attributed to an H-substance, which is either histamine or a histamine-like substance, liberated from injured cells. But this may not be true in all cases. Unless some irritating foreign body or crust is removed scratching is a poor remedy. Itching may be provoked without peripheral impulses by morphine. Epinephrine may inhibit responses to itch stimuli on local injection.

Reference: S. Rothman, *Physiological Reviews*, 21: 357-381 (1941).

## J

### JACKSONIAN EPILEPSY

See Epilepsy.

### JACOBY REAGENT AND TEST FOR PEPSIN AND TRYPSIN

1 cc. of pepsin in 0.56% hydrochloric acid is mixed with 2-3 cc. of reagent (1 gm. ricin and 1.5 gm. sodium chloride in 100 cc. water) and kept at incubator temperature. Even with as little as 0.01 mg. pepsin the mixture is made perfectly clear in a few hours.

Reference: Biochem. Zeit. 1, 71 (1906); 10, 228 (1908).

### JAFFE REACTION FOR CREATININE

A yellow-red to dark blood-red color is obtained when aqueous picric acid and sodium hydroxide solution are added to the test solution. Sensitivity—1:200000, the intensity of the color depends upon the amount of creatinine present. Creatine does not interfere, free acids do.

Reference: Zeit. physiol. Chem. 10, 399. Pharm. J. 54, 360 (1895).

See Creatine and Creatinine Metabolism.

### JAFFE TEST FOR KYNURENIC ACID

Tetrachlorhydroxykynurin, formed by heating kynurenic acid with potassium chlorate and hydrochloric acid, forms, with ammonia, a brown color changing gradually to green and dark blue.

Reference: Zeit. physiol. Chem. 7, 399. Ber. 38, 2713 (1905).

### JAKSCH TEST FOR MELANIN AND MELANOGEN IN URINE

These substances, with dilute ferric chloride solution, form a black precipitate which is soluble only in potassium hydroxide and concentrated acids.

Reference: Zeit. physiol. Chem. 13, 385.

### JALAPIN

$C_{34}H_{56}O_{16}$ ; scammonin; orizabin; a glucoside of Jalapa Oriza benzis; consisting of glucose and jalapinic acid; a colorless, amorphous solid, melting between 130-150°, used as a purgative.

### JAMESTOWN WEED

See Stramonium.

### JANSEN TEST FOR VITAMIN B<sub>1</sub>

A solution of 0.001-0.02 mg. vitamin B<sub>1</sub> is diluted with methanol to 2 cc. to which are added 1 cc. 30% sodium hydroxide and 0.1 cc. potassium ferricyanide solution; 13 cc. isobutanol are added after about 2 minutes. After shaking and centrifuging 10 cc. of isobutanol (containing thiochrome) are placed in a photoelectric fluorometer standardized for thiochrome by using quinine in sulfuric acid.

Reference: Rec. trav. chim. 55, 1046 (1936).

# JAPANIC ACID

$C_{22}H_{42}O_4$ ; a saturated dibasic fatty acid found in Japan Wax or Sumach Wax.

# JAUNDICE

Icterus; yellow staining of the skin and underlying tissues due to bile pigments. Types are distinguished as subicterus, hemolytic icterus, obstructive icterus, hepatosis (parenchymatous) icterus and icterus of the new born. The appearance of icterus (pseudo-icterus) may be brought about by yellow coloring due to other causes, e.g. carotinemia, due to excessive carotene in the food or picric acid staining. Hemolytic icterus shows an increase of bilirubin A in the blood without choluria (bile acids in the urine). Obstructive jaundice may be calculous icterus, stenosis icterus or icterus due to pancreatic tumors. Bile salts are used as a choleric to promote bile flow and possible clearing of passage. Hepatosis icterus involves liver damage by drugs, infectious diseases, etc.

In this field tests have been developed for liver function, as the galactose, azorubin, bilirubin tests in urine, the icterus (or icteric) index, van den Bergh test, and sedimentation tests.

# JAUNDICE (HEMOLYTIC)

In this group are included (a) primary anemias such as a pernicious anemia, splenic anemia or Banti's disease; (b) icterus neonatorum; (c) familial icterus; (d) "disassociated jaundice." It includes such conditions as those in which either the bilirubin or bile salt is retained and reabsorbed into the blood, while the other is being excreted in the normal way.

Hemolytic icterus is characterized mainly by a high bilirubin content of the blood, but generally with no appearance of pigment in the urine.

# JAUNDICE (LATENT)

Is the stage of hyperbilirubinemia below the amount necessary to produce visible jaundice.

# JAUNDICE (TOXIC AND INFECTIVE)

This type includes icterus in (a) catarrhal jaundice; (b) spirochetal icterus; (c) sepsis; (d) acute yellow atrophy; (e) pneumonia; (f) some cases of poisoning. It seems probable, that both a damage to the liver cells, and obstruction in the bile passages from cholangitis, fluctuate in position of importance.

# JECORIC ACID

An 18 carbon unsaturated fatty acid with 3 double bonds.

# JECORIN

An old name for alcoholic liver extracts.

# JEJUNUM

See Gastro-Enterology.

# JELINEK TEST FOR MUSTARD GAS

Reagent — ammoniacal silver nitrate solution is added to a solution of isatin containing a small amount of concentrated ammonia. Mustard gas, on paper impregnated with the reagent, forms a Bordeaux red color. At room temperature characteristic color affects are produced after 1 hour, at 60-80° in one minute.

Reference: Bull soc. chim. 4, 1813 (1937).

# JIMSON WEED

See Stramonium.

**JIMPSON WEED**

See Stramonium.

**JOHNSON-CLAPP REAGENT  
FOR CYTOSINE, THYMINE  
AND URACIL**

A red color is obtained when these substances are treated with diazobenzenesulfonic acid in alkaline solution.

Reference: J. Biol. Chem. 5, 163 (1908). Zeit. physiol. Chem. 42, 512 (1904).

**JOLLES TEST FOR  
GLUCURONIC ACID IN URINE**

200-400 cc. of urine are completely precipitated with lead acetate and filtered; the washed precipitate is suspended in water, decomposed with hydrogen sulfide and filtered. The filtrate is evaporated to 20 cc. and used for the Tollen's reaction.

Reference: Zeit. physiol. Chem. 81, 205 (1912).

**JOLLES TEST FOR  
LEVULOSE IN URINE**

Diluted urine is boiled for 1 minute with 10 drops of 20% alcoholic diphenylamine and 1 cc. concentrated hydrochloric acid; a blue

color is obtained. Sensitivity — 0.05%.

Reference: Apoth.-Ztg. 1909, 719. Ber. deut. pharm. Ges. 19, 486 (1909).

**JONES-SMITH TEST FOR  
ROTENONE**

A mixture of 1 cc. of substance in acetone and 1 cc. of 1:1 nitric acid, after standing for  $\frac{1}{2}$ -1 minute, is treated with 1 cc. ammonia and 9 cc. water; a blue color is produced. Sensitivity—0.1 mg.

Reference: Ind. Eng. Chem. Anal. Ed. 5, 75 (1933).

**JORDAN-PRYDE TEST FOR  
FRUCTOSE OR OTHER  
KETOHEXOSES**

8-10 mg. of hexose are heated at 40° for  $\frac{1}{2}$  hour with 10 mg. recrystallized skatole in 10 cc. concentrated hydrochloric acid; an intense "permanganate" color is produced.

Reference: Biochem. J. 32, 279 (1938).

**JUNIPERIC ACID**

$C_{16}H_{32}O_8$ ; a saturated monohydroxy acid found in Juniper wax.

## K

### KAEMPFERITRIN

See Flavonol Glycosides.

### KAHLENBERG REACTION FOR CHOLESTEROL

Arsenic trichloride dissolves cholesterol producing a yellow color changing to cherry-red; isocholesterol gives a cobalt-blue color changing to green; phytosterol gives a colorless solution.

When cholesterol is added to a hot solution of arsenic trioxide in hydrochloric acid and heated to boiling, a red color forms in the lower part of the tube. Isocholesterol gives a violet color.

Reference. J. Biol. Chem. 52, 217 (1922).

### KAHN TEST FOR ARSPHENAMINE INJURIES

Reagent—2% solution of dimethylamino-benzaldehyde in water, acidified with hydrochloric acid (Ehrlich-Kozlezkowsky solution). A red color is obtained when cold urine is treated with 2 drops of reagent, indicating injuries due to arspenamine treatment.

Reference: Münch. med. Wochschr. 1923, 431.

### KALLIKREIN

A supposed pancreatic hormone which causes increase of pulse amplitude and peristalsis; dilates peripheral blood vessels and lowers pressure; padutin.

### KAMNITZER-JOSEPH TEST FOR PREGNANCY

In early stages of pregnancy sugar appears in the urine following intramuscular injection of 1 cc. 0.2% phlorizin solution and 1 mg.  $\beta$ -eucaine. No sugar is found in non-pregnant women.

Reference: Therap. Gegenwart 1921, 321, 459. Klin. Wochschr. 1922, 889.

### KAPELLER-ADLER METHOD

A specific test for histidine. The black derivative obtained on brominating histidine is dissolved in ammonia or ammonium carbonate, the former giving a purplish red color, the latter a blue-violet color.

### KAPELER-ADLER TEST FOR PREGNANCY

A mixture of urine and a solution of 1 part of bromine in 100 parts 33% acetic acid is saturated with a mixture of 2 parts concentrated ammonia and 1 part 10% ammonium carbonate solution. A reddish to violet-red color, denoting histidine, is obtained, the shade depending upon the quantity present. A yellow to brownish-yellow color indicates a negative test.

Reference: Biochem. Zeit. 264, 131 (1933).

### KATABOLISM

See Catabolism.



**KAWAHARA TEST FOR  
PEPSIN**

Congo red, in the digestive fluid, changes from fuchsin red to violet to blue, the change toward blue depending upon the amount of pepsin present. For digestion, a boiled and filtered 0.05% solution of egg albumin or casein is used.

Reference: Arch. ges. Physiol. 206, 360 (1924).

**KEFIR**

A preparation of milk acted upon by kefir grains or fungi which are small, irregular, yellowish granules of a gelatinous consistency, used in the Caucasus for fermenting milk.

**KELLER REACTION**

See Digitalis.

**KELLY TEST FOR  
EPHEDRA ALKALOIDS**

2 gm. of air-dried drug are moistened with a 10% aqueous solution of sodium carbonate and ground with a few grains of clean, sharp sand in a mortar. The still damp material is placed in a continuous extractor and extracted with chloroform for 1 hour; the extract is shaken with 10 cc. 10% hydrochloric acid in a 25 cc. separatory funnel. The acid solution is heated with decolorizing charcoal for a few minutes and filtered. The solution is made strongly alkaline with 20% sodium hydroxide and then treated with 0.1 cc. of 2% copper sulfate solution; a typical blue or blue-violet color is obtained.

Reference: Am. J. Pharm. 109, 36 (1938).

**KEPHALIN**

Cephalin.

**KERASIN**

$C_{48}H_{98}O_8N$ ; m.p. 180°, levorotory; a cerebroside whose fatty acid is lignoceric acid, found in brain and nerve tissue.

**KERATIN**

Proteins of epidermal origin occurring in skin, fingernails, horns, hairs, hooves, and feathers. They are resistant to mechanical and chemical attack, insoluble in dilute acids and alkalis, water and organic solvents; not digestible by pepsin or trypsin.

See Protein Structure.

**KERATIN, ALPHA**

See Protein Structure.

**KERATIN, BETA**

See Protein Structure.

**KERATINS**

See Hair.

**KERATOHYALIN**

An albuminoid found in granules in the deepest layer of the epidermis, the stratum germinativum, probably a precursor of keratin.

**KETOGENESIS**

The production of acetone bodies, (acetone, beta hydroxybutyric acid, acetoacetic acid) that accompanies faulty fat metabolism. Found in diabetes, infections and wherever carbohydrate metabolism is disturbed. Resumption of normal carbohydrate metabolism results in cessation of acetone bodies. Amino acids, notably leucine and tyrosine can be ketogenic in severe diabetes. The keto acids drain the alkali reserve as they are neutralized by the alkali and excreted.

See Ketogenic — antiketogenic balance.

**KETOGENIC**

**ANTI-KETOGENIC BALANCE**

1 gram of protein produces 2.4

## K

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Cephalin.

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$C_{48}H_{98}O_8N$ ; m.p. 180°, levorotory; a cerebroside whose fatty acid is lignoceric acid, found in brain and nerve tissue.

# KERATIN

Proteins of epidermal origin occurring in skin, fingernails, horns, hairs, hooves, and feathers. They are resistant to mechanical and chemical attack, insoluble in dilute acids and alkalis, water and organic solvents; not digestible by pepsin or trypsin.

See Protein Structure.

# KERATIN, ALPHA

See Protein Structure.

# KERATIN, BETA

See Protein Structure.

# KERATINS

See Hair.

# KERATOHYALIN

An albuminoid found in granules in the deepest layer of the epidermis, the stratum germinativum, probably a precursor of keratin.

# KETOGENESIS

The production of acetone bodies, (acetone, beta hydroxybutyric acid, acetoacetic acid) that accompanies faulty fat metabolism. Found in diabetes, infections and wherever carbohydrate metabolism is disturbed. Resumption of normal carbohydrate metabolism results in cessation of acetone bodies. Amino acids, notably leucine and tyrosine can be ketogenic in severe diabetes. The keto acids drain the alkali reserve as they are neutralized by the alkali and excreted.

See Ketogenic — antiketogenic balance.

# KETOGENIC

# ANTI-KETOGENIC BALANCE

1 gram of protein produces 2.4

millimoles, 1 gram of fat 3.43 millimoles of ketogenic material. 1 gram of glucose produces 5.56, 1 gr. of protein 3.2, 1 gr. of fat 0.57 millimoles of antiketogenic material. The ratio

$$R = \frac{2.4P + 3.43F}{3.2P + 0.57F + 5.56G}$$

where P, F, and G are grams of protein, fat and glucose metabolized, is useful in determining diets to produce or prevent ketosis. If R is greater than 2, acidosis and ketosis results.

#### KETONE TEST

See Dakin.

#### KETOSE SUGAR

A sugar containing a group which is a ketone or potentially a ketone.

#### KETOSE TESTS

See Denigès, Votocek.

#### KETOSIS

The condition produced by failure to oxidize the acetone bodies. Depletion of reserve alkali and ammonia results.

#### KHOUVINE ORGANISM

See Cellulose Decomposition.

#### KIDNEY, HEMORRHAGIC

See Choline.

#### KIDNEY INSUFFICIENCY

See Becher.

#### KILIANI REACTION

See Digitalis.

#### KILIANI SYNTHESIS

The reaction of aldehydes and ketones with HCN to give nitriles which on hydrolysis yield an acid with one carbon more than the original compound.

#### KILOCALORY

Thousand calories. The term "large calory" is obsolescent. The term "kilogramcalory" is a misnomer.

M. K.

#### KINASE

A substance which converts the inactive form of an enzyme into its active form.

#### KINIC ACID

See Quinic Acid.

#### KINNERSLEY-PETERS TEST FOR VITAMIN B<sub>1</sub>

0.5 cc. diazotized sulfanilic acid are mixed with 1.25 cc. of a solution of 5.76 gm. sodium bicarbonate in 100 cc. water mixed with 100 cc. N sodium hydroxide. After one minute, 1 drop 40% formaldehyde is added, followed immediately with 0.3 cc. of vitamin B<sub>1</sub> (pH not lower than 3.5); a pink color developing in intensity for ½-1 hour is produced. Sensitivity—1.5-2 micrograms.

Reference: Biochem. J. 28, 667 (1934).

#### KISCH TEST FOR ADRENALINE AND TYROSINE

4.5 cc. of neutral test solution are treated with 0.5 cc. of 0.02 N hydrochloric acid and 0.2 cc. 1% sodium nitrite solution and heated on a steam bath for 10 minutes; adrenaline gives a rose to ruby-red color, depending upon the quantity. Tyrosine gives a yellow color changing to rose, to violet and finally to green.

Reference: Zeit. anal. Chem. 1934, 379.

#### KISSER REAGENT FOR CALCIUM

Soluble calcium salts in plants form characteristic crystals with a 0.264% aqueous picrolonic acid solution.

Reference: Mikrochemie 1, 25 (1923). Zeit. anal. Chem. 88, 417 (1932).

# KLEBS-LOEFFLER BACILLUS

See Microbiology.

# KNOOP'S DEAMINATION THEORY

A theory to explain the degradation mechanism of the amino-acids. The  $\alpha$ -amino acid is acted on by dehydrogenases, yielding an imine, the double bond of which adds on HOH, giving a hydroxy-amine, which then loses  $\text{NH}_3$ , yielding an  $\alpha$ -keto acid.

# KNOOP'S HISTIDINE REACTION

A test for histidine based on the formation of a reddish brown color when bromine is added to an acid solution of histidine and then the mixture is boiled.

# KNOOP $\beta$ -OXIDATION THEORY

See Carbohydrate and Fat Catabolism.

# KOBERT REACTIONS FOR SAPONINS

Ferric ferricyanide (made by mixing solutions of ferric chloride and potassium ferricyanide) turns blue on reduction by saponins. Saponin-copper is precipitated from Fehling's solution in the cold or on warming. Some saponins give a green color with Fehling's solution, even at high dilutions. Nickel and cobalt salt solutions give yellow colors with saponin. Mercuric chloride is reduced to calomel when heated with saponin; all saponins form a red color with concentrated sulfuric acid in the presence of air. With Fröhde's reagent, some saponins form a yellow color; some give a blue-green color with a green fluorescence with sulfuric acid containing ferric chloride and alcohol.

Reference: Süddeut. Apoth.-Ztg. 1900, 397.

# KOCH TEST FOR CHOLERA BACILLI

The addition of sulfuric acid to a culture of cholera bacilli produces a red color, due to the action of the acid on the metabolism products,—indole and nitrite.

Reference: Zeit. wiss. Mikroskop. 1894, 407.

# KOESSLER-HANKE ESTIMATION OF IMIDAZOLES

On the basis of the color produced by the reaction of the imidazole ring with phenyl diazonium sulfonate in alkaline medium, histidine, histamine, imidazole propionic and acetic acids and methylimidazole may be determined in quantities ranging from 0.001-0.05 mg.

Reference: J. Biol. Chem. 39, 497 (1919); 50, 235 (1922).

# KOESSLER & HANKE METHOD

A method for the determination of histidine based on the color produced by the imidazole ring of the histidine and p-diazo-benzene sulfonate.

# KOETTSTORFER NUMBER

Saponification number.

# KOJI

A culture of a micro-organism active in the hydrolysis of starch; see Taka-Diastase.

# KOJIC ACID

5-hydroxy-2-hydroxymethyl- $\alpha$ -pyrone, produced by *Aspergillus flavus-oryzae* moulds on glucose.

# KOLA

Dried cotyledons of *Cola nitida* containing caffeine and other

material and used as tonic, stimulant, diuretic.

### KOLISCH REAGENT FOR CREATININE

The solution contains 1 gm. sodium acetate, 30 gm. mercuric chloride and 3 drops of glacial acetic acid in 125 cc. of absolute alcohol.

Reference: Zent. inn. Med. 1895, 265. Chem. News 55, 304 (1887).

### KOLTHOFF REAGENTS AND TESTS FOR SODIUM

(1) Magnesium uranyl acetate—10 gm. uranyl acetate and 6 gm. 30% acetic acid are dissolved in water and diluted to 50 cc. 6 gm. acetic acid and 33 gm. magnesium acetate are dissolved in water and diluted to 50 cc. The solutions are mixed and, after several days, filtered. 2 cc. of test solution are treated with 10 drops of reagent and 2 cc. alcohol; a turbidity or precipitate forms within 1 hour, if more than 50 mg. sodium per liter are present.

(2) Zinc uranyl acetate—A hot solution of 10 gm. uranyl acetate and 6 gm. 30% acetic acid in 34 gm. water is mixed with a hot solution of 30 gm. zinc acetate and 3 gm. acetic acid in 17 gm. water and filtered after one day. When 0.5 cc. of test solution are mixed with 4 cc. of reagent, a crystalline precipitate is obtained, the time of formation depending on the quantity of sodium. With 50 mg. sodium per liter, precipitation occurs within  $\frac{1}{2}$  hour; alcohol sensitizes the test.

Reference. Pharm. Weekblad 1923, 1251. Zeit. anal. Chem. 70, 398 (1927).

### KOMBIC ACID

See Strophanthus.

### KOMM-BÖRINGER REACTION FOR TRYPTOPHANE AND ALANINE

5 cc. 15% hydrochloric acid, each 500 cc. of which contains 6 cc. 0.1% formaldehyde solution, are mixed with 5 cc. of tryptophane or albumin solution and the mixture is floated on 10 cc. 90% sulfuric acid and stirred slowly. A violet color, sensitivity 1:175000, is obtained which may also be used for colorimetric estimation. Formaldehyde may be advantageously replaced by a 0.25% p-dimethylaminobenzaldehyde solution in 10% hydrochloric acid; 22 cc. of test solution are treated with 2 cc. of reagent and 6 cc. 10% hydrochloric acid.

Reference: Zeit. physiol. Chem. 124, 287 (1923); 156, 35 (1926).

### KOSCIS-BUGHI TEST FOR FOLLICULIN

Even 0.001 mg. folliculin may be detected by the fluorescence obtained when 1 cc. of an aqueous or alcoholic solution is treated with concentrated sulfuric acid; the color is visible under filtered ultra-violet light. With oils, the test may be carried out after saponification with 50% sodium hydroxide; 2 layers are obtained after shaking 5-10 minutes, the test being made with the upper layer.

Reference: Mikrochim. Acta 2, 291 (1937).

### KOSSEL REACTION FOR ADENINE AND HYPOXANTHINE

The substance is heated on the steam bath for  $\frac{1}{2}$  hour with zinc and hydrochloric acid; the solution forms a red to reddish-brown color on addition of sodium chloride solution.



Reference: Zeit. physiol. Chem. 10, 250; 12, 241, 249.

# KOSSEL-PATTEN TEST FOR HISTIDINE

The addition of mercury salts to histidine solutions results in the formation of precipitates.

Reference: Zeit. physiol. Chem. 25, 165; 38, 39.

# KOSSEL'S HYPOTHESIS

See "Kossel's Protamine nucleus hypothesis."

# KOSSEL'S "PROTAMINE NUCLEUS" HYPOTHESIS

In 1896 Kossel stated that the proteins all have protamine nuclei, i.e. are largely arginine, histidine or lysine. In 1928 Larmour found that the correlation between the total basic nitrogen and the nitrogen of these three amino acids was quite high in a number of proteins and protein fractions.

# KOVACS TEST FOR INDOLE IN BACTERIAL CULTURES

A cherry-red color is obtained when drops of the reagent (5 gm. p-dimethylaminobenzaldehyde in 75 gm. amyl alcohol and 25 gm. hydrochloric acid) are floated on the culture.

Reference: Zeit. Immunitäts exp. Therap. 55, 311 (1928).

# KRAUSKOPF-RITTER REACTION FOR RESORCINOL

A dark green color is obtained when a 1:50000 aqueous solution of resorcinol is shaken with ammoniacal cobalt solution. Phenol, pyrocatechol, hydroquinone and pyrogallol do not interfere.

Reference: J.A.C.S. 38, 2182 (1916).

# KRAUSS TEST FOR MELANIN IN URINE

Melanin-containing urine gives a

deep black color with ferric ammonium sulfate solution.

Reference: Münch. med. Wochschr. 1924, 1704.

# KREBS CITRIC ACID CYCLE

See Carbohydrate and Fat Catabolism.

# KREIS REACTION FOR CHOLESTEROL AND PHYTOSTEROL

Several drops of an ether solution of the substances are evaporated and treated with 3 drops of a solution of 20 gm. benzaldehyde in 80 gm. absolute alcohol. The addition of concentrated sulfuric acid gives rise to a red-violet to dark violet color.

Reference: Chem.-Ztg. 1899, 21.

# KREIS TEST

A color test for rancidity in a fat due to oxidation. It depends on the formation of epihydrin aldehyde on the addition of ether, HCl and phloroglucinol to the fat.

# KRUEGER ACTIVITY TITRATION

See Bacteriophage.

# KRÜGER REACTION FOR ADENINE

A solution of 2 moles sodium hydroxide and 1 mole adenine are added to a solution of 1 mole of lead acetate. Microscopic crystals of adenine lead,  $C_5H_3N_5Pb$ , are obtained.

Reference: Zeit. physiol. Chem. 18, 430.

# KUHN TEST FOR BILE PIGMENTS IN URINE

Reagent—(1) Mixture of 10 cc. of 20% ammonia and 20 cc. of 5% copper sulfate solution. (2) Mixture of 20 cc. of 85% phosphoric acid and 20 cc. water. 2 cc. of (1) and 2 cc. of (2) are

added to 20 cc. urine, followed by 6 drops of toluene. After shaking and allowing to stand a few minutes, 4 cc. of alcohol are floated on the solution; a green color in the alcohol is obtained; a pink, blue or brown-gray color is negative.

Reference: J. pharm. chim. [8] 8, 546 (1928).

#### KYNURENIC ACID

4 - hydroxy - quinoline - 2 - car-

boxylic acid, found in dog urine as a product of the metabolism of tryptophane.

#### KYNURENIC ACID TEST

See Hofmeister, Jaffé.

#### KYNURENIN

$(\text{NH}_2)\text{C}_6\text{H}_5\text{C}(\text{COOH})=\text{CH}\cdot\text{CH}\cdot\text{NH}\cdot\text{COOH}$ ; a compound found in rabbit urine, resulting from feeding large amounts of tryptophane, and supposed to be a normal intermediate in its metabolism.

## L

### LABAT REACTION FOR HORDENINE AND METHENAMINE

An emerald-green color is obtained when a mixture of 1 cc. of 1% hordenine solution, 1 cc. of 1% methenamine solution and 2 cc. sulfuric acid are heated to boiling. Sensitivity — hordenine 0.1 mg.; methenamine 0.001%.

Reference: J. pharm. chim. 1909, 433.

### LABAT TEST FOR LACTOSE IN URINE

100 cc. of slightly ammoniacal urine are evaporated to 10 cc. on the water bath, filtered, clarified with lead subacetate and re-filtered. This is treated with an equal volume of a solution of 1 cc. phenylhydrazine, 3 cc. glacial acetic acid and 20 cc. sodium acetate soln. After heating on a steam bath for  $\frac{1}{2}$  hour and cooling, the characteristic lactosazone may be identified microscopically.

Reference: Bull. trav. soc. pharm. Bordeaux 1910, 342.

### LABURNINE

See Cytisine.

### LACCA

See Shellac.

### LACCASE

Enzyme of bacteria and mushrooms responsible for converting polyphenols to their quinones.

### LACTACIDOGEN

An old name for the Harden-Young ester and a little used name for the Neuberg ester.

### LACTALBUMIN

An albumin found in milk; it consists largely of lactoglobulin; m.w. about 17500.

### LACTASE

A carbohydrase that hydrolyzes lactose to galactose and glucose, and also  $\beta$ -galactosides.

See Enzymes, Non-Proteolytic.

### LACTATION DISTURBANCES

The disturbances of the period of milk formation following childbirth. These include agalactia, polygalactia, galactorrhea, fissure of nipple and mastitis. Agalactia is a deficiency or absence of milk which may be due to defective development, malnutrition, disease or emotional disturbance. Polygalactia is an abnormal increase of milk which is prolonged. Galactorrhea is a profuse flow which does not stop till a return to menstruation. Fissure threatens abscess formation. Mastitis proper is an abnormal distension which may occur in the infant as well as in the nursing woman due to infection or injury in massage. The mastitis may be parenchymatous or interstitial. Milk secretion often has to be interrupted, e.g. by belladonna administration.

**LACTATION,  
SUPPRESSION OF**

See Estrogens, Synthetic.

**LACTESCENCE**

The milky appearance of serum due to large numbers of chylomicrons.

**LACTIC ACIDS**

2 optically active isomers of alpha-hydroxypropionic acid and their racemic mixture; d-lactic acid, sarcolactic acid, occurs in muscle, and is a product of carbohydrate metabolism.

See Carbohydrate Metabolism.

**LACTIC ACID CYCLE**

See Carbohydrate Metabolism.

**LACTIC ACID TEST  
(IN PHARMACEUTICALS)**

See Arny-Dimler.

**LACTIC ACID TESTS**

See Eegriwe, Hopkins.

**LACTIC DEHYDROGENASE  
(BACT. COLI)**

An enzyme of the autolysate of Bact. coli which catalyzes the oxidation of lactic acid and alpha-hydroxybutyric acid.

**LACTIC DEHYDROGENASE  
(GONOCOCCUS)**

A cytochrome-reducing dehydrogenase which catalyzes the oxidation of the l-forms of lactic and alpha-hydroxybutyric acids to their corresponding keto acids.

**LACTIC DEHYDROGENASE  
(YEAST)**

A cytochrome-reducing dehydrogenase which catalyzes the oxidation of lactic and alpha-hydroxybutyric acids to their keto acids (10 forms), but no coenzyme is necessary.

**LACTIC ENZYME**

The enzyme which catalyzes the

oxidation of l(+)-lactate to pyruvate; a pyridinoprotein, extracted from skeletal muscle of rabbit.

**LACTOCHROME**

Vitamin B<sub>2</sub>.

**LACTOFLAVIN**

Riboflavin; see Vitamin B<sub>2</sub>.

**LACTOGLOBULIN**

A globulin of milk; molecular weight 39000; 341 peptide linkages have been estimated per molecule.

**LACTOL**

A term loosely used for ring modifications of sugars as well as for various other ring structures, which is yielding the field entirely to the terms pyranose and furanose.

**LACTOSE**

The reducing disaccharide of milk, which is prepared commercially from milk whey. It is glucopyranose-4-β-galactopyranoside.

**LACTOSE, TEST FOR  
(IN URINE)**

See Labat.

**LACTOSURIA**

The excretion of lactose in the urine of lactating women or of infants.

See Glycosurias, Non-Diabetic.

**LAFON REACTION**

See Digitalis.

**LAMBRECHT REACTION  
FOR PHLORIDZIN**

One drop of a 1% alcoholic solution of α-nitroso-β-naphthol and 3 drops concentrated sulfuric acid are added to 2 cc. of solution (0.5-500 mg. phloridzin per liter), heated to boiling, cooled rapidly, treated with 3 cc. of ether and 1 cc. alcohol and shaken. An unstable red coloration is obtained.

Reference: Compt. rend. soc. biol. 124, 263 (1937).

**LAMELLIBRANCHIATA**

See Mollusca.

**LANADIGINE**

See Digitalis.

**LANATOSIDES A, B and C**

See Digitalis.

**LANDSTEINER REACTION FOR TYROSINE**

A hydrochloric acid solution of tyrosine is treated with a sodium nitrite solution, made alkaline and treated with  $\alpha$ -naphthol, yielding a blue-red color.

Reference: Zentr. Physiol. 1894, 773; 1895, 434.

**LANGE'S TEST**

A test for the presence of protein-globulin in the cerebrospinal fluid, and thus for the diagnosis of cerebrospinal syphilis.

**LANGLEY-ALBRECHT REACTION FOR FLAVIANIC ACID**

An orange-red color is produced when the acid is reduced with metal and acid and reoxidized by air in alkaline medium.

Reference: J. Biol. Chem. 108, 729 (1935).

**LANOCERIC ACID**

$C_{30}H_{60}O_4$ ; a saturated dihydroxy fatty acid found in lanolin; m.p. 104-105°, purity doubted.

**LANOLIN**

A crude extract of sterols from wool grease.

**LANOMYRISTIC ACID**

$C_{14}H_{28}O_2$ ; an acid of wool grease.

**LANOPALMITIC ACID**

$C_{16}H_{32}O_2$ ; a saturated monohydroxy fatty acid found in lanolin.

**LANOSTEROL**

$C_{30}H_{50}O$ ; a pentacyclic sterol with

two double bonds found in lanolin; m.p. 141°. H. S.

**LANTHIONINE**

Cystine minus one sulfur atom, a conversion product of cystine in proteins by alkali.

**LARICIC ACID**

See Agaricin.

**LARSON REACTION FOR CHOLESTEROL**

A 25% chloroform solution of antimony pentachloride stains cholesterol and its esters a dark brown color.

Reference: J. Lab. Clin. Med. 18, 249 (1933).

**LAUDANUM**

See Opium.

**LAURIC ACID**

$CH_3(CH_2)_{10}COOH$ ; m.p. 47-48°; a saturated fatty acid found in laurel oil.

**LECITHASE**

Group of enzymes capable of splitting off fatty acids or choline phosphate group from lecithins.

**LECITHIN**

Any ester of choline, glycerol and phosphoric acid; richly distributed in nervous tissue and also essential to all cells; soluble in water with formation of colloids, and most organic solvents except acetone.

**LECITHINASES**

See Enzymes, Non-Proteolytic.

**LECITHIN TESTS**

See Casanova, Orlow, Raspail, Romieu, Sanchez.

**LECITHOPROTEINS**

In the American classification of proteins the lecithoproteins are conjugated proteins where the additional group is lecithin or a phospholipid.

Examples: proteins of the cytoplasm and tissue fibrinogen.

# **LEGAL NITROPRUSSIDE REACTION**

See Digitalis.

# **LEGAL REACTION FOR SKATOLE AND INDOLE**

A 1:1000 solution of indole is treated with sodium nitroprusside until yellow, then sodium hydroxide is added; a violet-blue color changing to pure blue on the addition of hydrochloric or acetic acid is formed. Sensitivity—1:100000. With skatole, a yellow color is obtained on similar treatment. On boiling with  $\frac{1}{4}$  the volume of acetic acid, a violet color forms gradually.

Reference: Zeit. physiol. Chem. 1883, 447. Zentr. ges. inn. Med. 1912, 111, 55.

# **LEGAL TEST FOR ACETONE IN URINE**

The urine or its distillate is treated with freshly prepared sodium nitroprusside solution; a red color soon changing to yellow is obtained if acetone is present. With an excess of acetic acid, a carmine-red color is formed, changing to violet, then blue on standing.

Reference: Jahresber. Schlesich. Ges. vaterl. Kultur 1882, 89. Breslauer ärztl. Zeit. 1883 Nos. 3-4. Chem.-Ztg. 1898, 127.

# **LEGUMELIN**

An albumin of the seeds of leguminous plants, such as peas or vetches.

# **LEGUMIN**

A globulin of leguminous plant seeds, such as peas and vetches.

# **LEJEUNE TEST FOR BENZOYL PEROXIDE IN BLEACHED FLOUR**

Reagent—2.5 gm. p-diaminodiphenylamine sulfate is agitated with 250 cc. alcohol for one hour and allowed to stand overnight. A mixture of 0.7 gm. flour, 2.5 cc. petroleum benzine and 1 cc. reagent is well agitated and allowed to stand. A bluish-green color develops in the supernatant liquid.

Reference: Ing. chim. 17, 30 (1929).

# **LENS**

See Eye, Biochemistry of.

# **LEPRA**

See Leprosy.

# **LEPROSY**

Leprosy; elephantiasis graecorum; a chronic, infectious, contagious disease caused by Mycobacterium leprae (Bacillus leprae) with a long period of incubation. It shows as neural leprosy, cutaneous leprosy and mixed types. Outstanding remedies are chaulmoogra and hydnocarpus oils and their derivatives taken internally or by injection.

# **LEPTOSOMIC PHYSIQUE**

See Psychiatry, Biochemistry of.

# **LETHAL DOSE, MINIMUM**

See Chemotherapy.

# **1-LEUCINE**

$C_6H_{13}O_2N$ ;  $\alpha$ -amino isocaproic acid, i.p. 6.05, m.p. 293-295°; an indispensable amino acid of all proteins; colorless, shiny plates, slightly soluble in water, while impure crystals are spherical nodules, quite soluble in water.

# **LEUCINE METABOLISM**

Leucine is oxidized to 2-keto-4-methyl valeric acid, which is oxi-



dized to isovaleric acid, then demethylated to  $\beta$ -hydroxybutyric acid, which then undergoes oxidation. It is potentially ketogenic.

# **LEUCINE, RELATION TO STEROIDS**

See Steroids.

# **LEUCOCIDINS**

See Microbiology.

# **LEUCOCYTHEMIA**

See Leukemia.

# **LEUCO-FLAVOPROTEIN**

Reduced flavoprotein.

# **LEUCOPTERIN**

The white pigment of butterfly wings, a dipurine derivative with guanin residues.

# **LEUCOSIN**

An albumin of the seeds of rye, barley and wheat.

# **LEUCOTAXINE**

A substance assumed to be liberated by injured tissue, found in inflammatory exudates; a lower polypeptide with marked capillary dilating power, attracts leucocytes towards injured tissue.

# **LEUCOTOXIN**

See Immunological Phenomena.

# **LEUCOTRYPTASE**

See Wound Healing.

# **LEUKEMIA**

Leukocythemia; a disease of the leukocyte-producing tissues showing myelogenous, lymphatic and monocytic varieties. An outstanding symptom is enormous spleen enlargement. The blood picture shows a very high leucocyte count at certain stages and changes in red cells, hemoglobin and the quality of the cells with malformations. The disease has been called "blood cancer," is very deadly, and the treatment is only for the relief of symptoms.

# **LEUKOCYTE INCREASE IN BLOOD, TEST FOR**

See Mayer Reagent.

# **LEUKOCYTES**

White blood cells of a number of varieties existing in blood to the extent of 5000-10000 per cu. mm. They are essential in fighting disease, in which case there is a sharp increase in their number. This bactericidal property is partly due to the proteolytic and lipolytic enzymes contained in the leukocytes.

# **LEVAN**

A water soluble fructosan of various grasses.

# **LEVENE-BEATTY REAGENT FOR AMINO ACIDS**

A very concentrated solution of phosphotungstic acid (2-4 parts of acid to 1 part of water) precipitates concentrated solutions of alanine, aspartic acid, glycocoll, glutamic acid, leucine, etc. Reference: Zeit. physiol. Chem. 1906, 149.

# **LEVINE-BIEN TESTS FOR CAROTENE**

I. The addition of 3 cc. of a mixture of 1 vol. 37% formaldehyde and 50 vols. sulfuric acid to 3 cc. of a chloroform solution forms a deep violet zone at the contact zone. The color goes into the acid on shaking. Sensitivity—0.01 mg. in 2.5 cc.

II. The addition of 3 drops of a mixture of 9 parts of trichloroacetic acid and 1 part water to 0.1 cc. chloroform solution of carotene results in the immediate formation of an intense blue color, fading on the addition of water or alcohol, but not on heating.

III. 0.5 gm. chloral hydrate,

liquefied by heating, is treated with 1 drop hydrochloric acid and 0.1 cc. of a chloroform solution of substance; an immediate intense blue is given by carotene; ergosterol forms a carmine-red color changing to evanescent green and finally to a persistent blue.

Reference: Proc. Soc. Exptl. Biol. Med. 31, 581; 32, 335 (1934).

#### LEVINE-McKAY TEST FOR DIFFERENTIATING ERGOSTEROL FROM CHOLESTEROL

Reagent—1 vol. concentrated hydrochloric acid and 3 vols. 2% aqueous sodium selenite solution. 2 cc. of reagent and 2 cc. of a chloroform solution of ergosterol are heated, in a test tube, on the water bath until the chloroform is evaporated and 2 cc. of chloroform are added. A light yellow to deep orange color is given by ergosterol.

Reference: Proc. Soc. Exptl. Biol. Med. 33, 546 (1936).

#### LEVINE-RICHMAN REACTION FOR CHOLESTEROL

The chloroform solution of cholesterol is treated with an equal volume of concentrated sulfuric acid containing 125 mg. sodium selenite per 25 cc. acid. The top layer becomes deep purple, the bottom layer turns red-brown to very dark brown without green fluorescence. Sensitivity—0.001%.

Reference: Proc. Soc. Exptl. Biol. Med. 27, 832 (1930).

#### LEVO (l-) ROTATORY

The rotation of the plane of polarized light to the left, shown by solutions of many optically active compounds.

#### LEVULIC ACID

See Levulinic Acid.

#### LEVULINIC ACID

$\text{CH}_3\text{COCH}_2\text{CH}_2\text{COOH}$ ; m.p.  $33.1^\circ$ ;  $\beta$ -acetylpropionic acid; a keto-fatty acid found resulting from carbohydrate metabolism.

#### LEVULOSE

See Fructose.

See also Glycosurias, Non-Diabetic.

#### LEVULOSE TESTS

See Brown-Lum, Jolles, Jordan-Pryde, Seliwanoff, Sugahara, Wagenaar.

#### LEWIN REACTION FOR PROTEINS

Proteins form a violet color with an 0.1% solution of triformoxime (trioximino-methylene) in concentrated sulfuric acid. A similar, but less sensitive, reaction is given by paraformaldehyde.

Reference: Ber. 46, 1796 (1913).

#### L.H.

Luteinizing hormone.

#### LIBERALLI TEST FOR HYDROXY ACIDS

Reagent—32.4 cc. 10% ferric chloride solution, 58.2 cc. 10% potassium thiocyanate solution diluted with water to 100 cc. Neutral solutions of hydroxy acids turn the reagent yellow. The same color is given by acetic and oxalic acids. The addition of 1 drop of nitric acid gives a red color with hydroxy acids, but not with others.

Reference: Biol. assoc. brasil. farm. 12, 24 (1931).

#### LICHENASE

A polyase which splits lichenin to cellobiose; found in malt extracts, snail intestine, etc.

See Enzymes, Non-Proteolytic.

# LICHENIN

Moss starch; a carbohydrate,  $C_6H_{10}O_5$ , from Iceland moss, used as demulcent.

# LIEBERMANN-BURCHARD REACTION

A test for unsaturated sterols based on the green color formed when the sterol is treated with chloroform, acetic anhydride and concentrated sulfuric acid.

# LIEBERMANN'S REACTION

A test for most proteins and specific for tryptophane or indole derivatives. Heat the protein with conc. HCl whereupon a violet to blue-black color develops.

# LIEBERMANN TEST FOR ETHYL SULFIDE IN URINE

Reagent—8 gm. potassium nitrite are dissolved in 100 gm. concentrated sulfuric acid containing 6-7 cc. water and the liquid separated from the crystals by decantation through glass wool. Ethyl sulfide colors the reagent a transitory green.

Reference: Ber. 20, 3232 (1887).

# LIEBERMANN TEST FOR PHYTOSTEROL AND CHOLESTEROL

Concentrated sulfuric acid is added dropwise to a cold concentrated acetic anhydride solution of the sterol giving the following color reactions: rose-red to blue to green for cholesterol from gallstones; rose-red to blue to green for phytosterol from cottonseed oil; same for phytosterol from belladonna leaves and grass leaves. Onocol and onoketone give brownish-yellow to reddish-brown to green.

Reference: Ber. 18, 804 (1885).

# LIEBERMANN TEST FOR PROTEINS

A violet-blue color is obtained when alcohol and ether washed protein is treated with hot, concentrated hydrochloric acid. Substances containing the tryptophane group give this reaction.

Reference: Zeit. anal. Chem. 26, 674 (1887); 42, 190 (1903). J. Physiol. 30, 311 (1903).

# LIEBERMANN-VOGT REACTION FOR COD LIVER OIL

A cooled mixture of 20 drops chloroform, 40 drops acetic anhydride and 3 drops sulfuric acid are treated with 3 drops cod liver oil and shaken; an intense blue color, disappearing rapidly is obtained. In 20-40 seconds a permanent olive green is formed.

Reference: Wochschr. Chem. Pharm. 1905, 674.

# LIESEGANG PHENOMENA

If one compound, such as potassium chromate is dissolved in a gelatin gel and a solution of another substance, such as silver nitrate is allowed to diffuse into the gel, the precipitate which forms (silver chromate) forms a series of concentric rings, separated by more or less clear portions of the gel. These rings are called Liesegang rings. No completely satisfactory explanation has been offered.

# LIFE, MATERIAL BASE OF

See Protoplasm.

# LIFSCHÜTZ REACTION FOR GYNOCARDIA OIL

One drop of oil is dissolved in 0.5 cc. chloroform, treated with 1.5 cc. glacial acetic acid and 4-5 drops concentrated sulfuric acid added. An intense grass-green

color, red-violet in transmitted light, forms gradually.

Reference: Chem.-Ztg. 45, 1264 (1921).

# **LIGHT-DENATURATION**

See Radiation, Biological Effects of.

# **LIGHT QUANTA**

See Photosynthesis.

# **LIGNIN**

A high molecular weight polymerized compound which occurs in plants together with cellulose and lends rigidity to the cell wall. The exact structure is in doubt but the weight of evidence tends towards a polymer of 12 molecules of coniferyl alcohol,  $3,4-(OH)_2C_6H_3(CH)_2CH_2OH$ .

# **LIGNOCERIC ACID**

A saturated fatty acid,  $CH_3(CH_2)_{22}COOH$ , found in glucolipids and arachis oil; m.p. 81-82°. A straight chain form is present in beechwood tar and peanut oil. A branched chain form is present in sphingomyelin and in keratin linked as a lipin.

# **LILACIN**

See Terpeneol.

# **LIMONENE**

d-limonene, a terpene, is found in lemon, orange, etc., oils; b.p. 176°. l-limonene is found in pine needle, peppermint, etc., oils; b.p. 176°.

# **LINAMARIN**

$C_{30}H_{50}O_{19}N_3$ ; phaseolunatin; a glycoside of flax seeds, rubber seeds and young plants, consisting of glucose and acetonecyanhydrin. It crystallizes in needles, m.p. 142°, and has been synthesized.

# **LINDERSTRÖM**

# **LANG'S TITRATION**

A method for quantitative analysis

of amino-acids, based on the fact that an amino acid or protein in 90% acetone does not contain the amino acid in the zwitterion form, thus enabling direct titration to be run with alcoholic HCl or alcoholic NaOH.

# **LINOLEIC ACID**

Linolic acid; an unsaturated fatty acid,  $CH_3(CH_2)_6CH:CH.CH:CH(CH_2)_6COOH$ , found in cottonseed oil, poppyseed and other vegetable oils. The double bonds add on oxygen from the air, forming a stable hard film, allowing it to be used as a drying oil. B.p. 229-230° at 16 mm., m.p. 11°.

# **LINOLENIC ACID**

An unsaturated fatty acid,  $CH_3(CH_2)_5CH:CH.CH:CH:CH(CH_2)_5COOH$  found in linseed oil. B.P. 230-232° at 17 mm.

# **LINOLIC ACID**

See Linoleic Acid.

# **LINOLOOL**

l-form of a terpene alcohol found in oil of linaloe; d-form found in orange and coriander oils; b.p. 198-199°.

# **LIPASE, PANCREATIC, TEST FOR**

See Ethyl Butyrate.

# **LIPASES**

A group of enzymes that hydrolyze the fatty acid esters of glycerol, the fats. The individual enzymes are usually named after the source of the enzyme, as pancreatic lipase. In the presence of specific concentrations of sodium taurocholate, liver and pancreatic lipases act more rapidly.

See Enzymes, Non-Proteolytic.

# **LIPIDS, CLASSIFICATION OF**

Bloor suggests classifying lipids as follows:

**Simple Lipids—**

1. Fats—esters of fatty acids with glycerol.
2. Waxes—esters of fatty acids with alcohols other than glycerol.

**Compound Lipids—**

1. Phospholipids—substituted fats containing phosphoric acid and nitrogen: lecithin, cephalin, sphingomyelin.
2. Glycolipids—compounds of the fatty acids with a carbohydrate and containing nitrogen but no phosphoric acid: phrenosin, kersin. (Also called cerebroside.)
3. Aminolipids, sulfolipids, etc.—groups which are at present not well established.

**Derived Lipids—**

1. Fatty acids.
2. Sterols.

See individual entries.

**LIPID SOLUBILITY**

See Permeability.

**LIPIDS (LIPIDES)**

A term used confusedly and interchangeably to designate fats, fatty substances, fats and lipoids, and lipins.

**LIPIDS, DERIVED**

A term applied to free fatty acids and sterols and other alcohols.

**LIPINS**

A term used like "lipids," but also restricted to nitrogen containing fatty substances.

**LIPOCAIC**

A hormone of the pancreas which counteracts the production of fatty liver which, however, may be due to choline or insulin and not to special hormone action.

**LIPOCHROMES**

An old name for carotenoids found in animal sources.

**LIPOCLASTIC**

See Lipolytic.

**LIPOCYTIC COEFFICIENT**

The percentage of lipide phosphorus as compared to total cholesterol; tends to a constant in animal tissue metabolism.

**LIPOIDOSES**

Diseases marked by heavy deposition of lipids in various organs, as Niemann-Pick's disease, Gaucher disease, Christian-Schueller disease, xanthomatoses.

**LIPOIDS**

Substances associated with fats; fatty compounds containing nitrogen; sometimes the term is made to include the fats.

**LIPOIDS AND MENTAL STATES**

See Psychiatry, Biochemistry of.

**LIPOITRIN EFFECT**

The decrease of blood fats.

**LIPOLYTIC**

Capable of hydrolysing fats; lipoclastic.

**LIPOPENIA**

A low level of blood fat, found in hyperthyroidism, and certain anemias.

**LIPOPROTEINS**

In the American classification of proteins, the lipoproteins are conjugated proteins where the additional group is a higher fatty acid.

**LIPOTROPISM**

See Choline.

**LIPP TEST FOR PROTEIN IN URINE**

Protein-containing urine is rendered turbid by powdered m-dihydroxybenzene.

Reference: Münch. med. Wochschr. 81, 1469 (1934).

**LIQUIDS, NEWTONIAN AND NON-NEWTONIAN**

See Protoplasm.

**LISON REAGENT FOR PEROXIDASES**

1.5 gm. acid fuchsin or acid violet are dissolved, with the aid of heat, in a mixture of 2 cc. glacial acetic acid and 100 cc. of water. Following the addition of 5 gm. of zinc dust, the solution is cooled and treated with 2 cc. glacial acetic acid; the solution is filtered before use and 1 cc. hydrogen peroxide added to each 10 cc.

Reference: Compt. rend. soc. biol. 106, 1266 (1931).

**LISON TEST FOR HEMOGLOBIN**

Treatment with a mixture of 2.5 gm. lead acetate, 10 cc. formaldehyde and 100 cc. water converts blood hemoglobin to hematin; peroxidases in the hemoglobin are unaffected but give a characteristic blue color with benzidine-hydrogen peroxide. The test is specific.

Reference: Rev. hyg. méd. prévent. 52, 894. Compt. rend. soc. biol. 103, 36 (1930).

**LITHOCHOLIC ACID**

$C_{24}H_{40}O_8$ ; m.p.  $186^{\circ}$ ; bile acid found in small quantities in man and in the ox. It is a 3-hydroxy cholanolic acid.

**LITHOTOMY**

See Urology.

**LIVER**

The largest organ in the body, weighing about 1800 gm., and probably performing a greater volume of duties than any other organ.

See Gastro-Enterology.

**LIVER ATROPHY**

A condition marked by destruc-

tion of liver cells caused by toxic agents or previous disease. Jaundice develops along with cerebral symptoms and shrinkage of the liver; also known as "acute yellow atrophy of the liver" or "diffuse toxic necrosis of the liver." Intensive carbohydrate administration is used.

**LIVER CIRRHOSES**

Chronic diseases of the liver usually due to obstruction, showing as (1) portal cirrhosis or chronic interstitial hepatitis and (2) biliary cirrhosis or hypertrophic biliary cirrhosis. The former is usually caused by alcoholism or bacterial toxins and spreads from the portal vein region; the latter shows in the bile passages and liver cells either as a primary process, icterus catarrhalis, or an obstructive type, infective cholangitis, with cholelithiasis.

**LIVER, FATE OF AMINO ACIDS IN**

See Amino Acids, Physiology of.

**LIVERS, FATTY**

See Choline.

**LIVER FLAVOPROTEIN**

A specific aldehyde oxidase of the liver having flavinadenine dinucleotide as the prosthetic group; utilizes molecular oxygen or other hydrogen acceptors, like methylene blue, cytochrome c, nitrate, etc.

**LIVER FUNCTION**

See Detoxication.

**LIVER FUNCTION TESTS**

See Bauer.

**LIVER OIL TEST**

See Tortelli-Gaffe.

**LIVER, PROTEIN LOSS OF**

See Autolysis.



**LIVETIN**

A protein of the egg yolk (about 20%), perhaps identical with the serum globulin of the hen.

**LLOYD REAGENT FOR ALKALOIDS**

Aluminum silicate precipitates alkaloids from neutral or acid solutions; by the use of alkali and organic solvents, the alkaloid may be extracted from the precipitate.

Reference: J.A.C.S. 27, 8 (1905).

**LOBELANIDINE**

$C_{22}H_{29}O_2N$ ; an alkaloid of Lobelia. Prismatic scales from alcohol, m.p.  $150^{\circ}$ . Oxidizes to dl-Lobeline, which it resembles in structure and physiological action.

**LOBELANINE**

$C_{22}H_{25}O_2N$ ; second most abundant of alkaloid of Lobelia. Needles from ether, m.p.  $99^{\circ}$ . Reduces with sodium amalgam to lobelanidine. Resembles dl-lobeline in physiological action.

**dl-LOBELINE**

$C_{22}H_{27}O_2N$ ; most active and abundant alkaloid of Lobelia. Crystallizes in prisms from alcohol, m.p.  $110^{\circ}$ . Oxidizes to lobelanine, reduces to lobelanidine. Respiratory stimulant; excites and then paralyzes the ganglia of the involuntary nervous system.

**LOBRY DE BRUIN TRANSFORMATION**

Sugar plus very dilute alkalis (0.05 N) at room temperature is converted to a series of isomers and the rotation of the solution is changed.

**LOGARITHMIC GROWTH**

See Growth.

**LOMBARDO TEST FOR MERCURY IN URINE**

A mixture of 1 drop egg albumin and 5 cc. of urine are shaken well and treated with 3 cc. freshly prepared stannous chloride solution to which some hydrochloric acid has been added. Centrifuge and observe microscopically with a magnification of 600; small globules of mercury may be observed.

Reference: Arch. farmacol. sper. 7, 400.

**LOMBIRINE**

See Digitalis.

**LOONEY TEST FOR CYSTINE IN URINE**

The addition of phosphotungstic acid and sodium sulfite produces a blue color with the test solution; other reducing agents give the same reaction.

Reference: J. Biol. Chem. 54, 171 (1922).

**LOTUSIN**

$C_{28}H_{31}O_{16}N$ ; a glycoside of Lotus arabicus consisting of HCN, a disaccharide and lotoflavin.

**LUCIFERASE**

See Bioluminescence.

**LUCIFERIN**

See Bioluminescence.

**LUGOL TEST FOR ALBUMIN IN URINE**

Albumin-containing urine forms a precipitate when treated with a solution of iodine-potassium iodide acidified with acetic acid. Reference: Zeit. physiol. Chem. 54, 355. J. Pharm. Soc. Japan 1900, 1163.

**LUMICHROM**

6:7-dimethyl alloxazine, formed from riboflavin on illumination in neutral solution in methanol.

**LUMIFLAVIN**

6 : 7 : 9 - trimethyl isoalloxazine,

formed by the illumination of ribo-flavin under alkaline conditions.

**LUMINAL**

Phenyl-ethyl-barbituric acid; trade name of a sedative also known as phenobarbital.

**LUMINESCENCE**

See Bioluminescence.

**LUMINOUS SPECIES**

See Bioluminescence.

**LUMISTEROL**

$C_{28}H_{44}O$ ; m.p.  $118^{\circ}$ ; an inert irradiation product of ergosterol, which on further irradiation yields tachysterol. H. S.

**LUPINIDINE**

See Sparteine.

**LUPININE**

$C_{10}H_{19}ON$ ; m.p.  $68-71^{\circ}$ ; alkaloid of yellow lupin seeds.

**LUTEIN**

(1) dried and powdered fully developed corpora lutea of the hog.  
(2) See Xanthophyll.

**LUTEINIZING HORMONE**

A hormone of the anterior pituitary that causes ovulation and luteinization in the female and the production of androgens in the male. The hormone is protein in structure.

**LUTOSE**

Polysaccharide obtained by hydrolysis of luteic acid, a product of the action of *Penicillium luteum* on a pentose or hexose.

**LUTOESTERONE**

See Progesterone.

**LYCACONITINE**

An alkaloid having a curare-like action.

**LYCOPENE**

$C_{46}H_{56}$ ; a red carotenoid hydrocarbon pigment found in fruit of

tomatoes, rose hips, berries; m.p.  $175^{\circ}$ ; soluble in chloroform and carbon sulfide.

**LYCOPODIC ACID**

A 16 carbon one double bond unsaturated fatty acid of lycopodium spores.

**LYMPH**

A colorless body fluid, found in the lymphatic channels, formed by permeation of blood plasma through the capillaries. Its chemical structure is similar to plasma, except for higher protein in the latter and the presence of larger numbers of lymphocytes in the former.

**LYMPHOCYTE**

A variety of white blood corpuscle which arises in the reticular tissue of the lymph glands and lymph nodes. The nucleus is single and is surrounded by protoplasm which is generally described as nongranular.

**LYO-AMYLASES**

Soluble amylases of the cell.

**LYOPHILIC**

A system in which the disperse phase and the dispersions medium are mutually more or less soluble in each other.

**LYOPHOBIC**

A system in which the disperse phase is insoluble in the dispersions medium, and the dispersions medium does not dissolve in the disperse phase.

**LYOTROPIC SERIES**

A list of equivalent ions, in the order of their ability to flocculate a sol. Essentially the same order holds for surface tension of molten salts of these ions and for the effect of these ions in increasing the surface tension of water,

probably due to the degree of hydration of the ion.

Also called the Hofmeister series.

**LYOTRYPSIN**

See Desmotrypsin.

**LYSERGIC ACID**

See Ergot.

**LYSIN**

See Immunological Phenomena.

**d-LYSINE**

$\alpha$ - $\epsilon$ -diamino caproic acid; i.p. 9.52; m.p. 224° (decomposes); an indispensable basic amino acid found in many proteins. It is a strong base and absorbs CO<sub>2</sub> from the air. See Amino Acids.

**LYSINE TEST**

See Herzog.

**LYSOCEPHALINS**

The hydrolytic products of cepha-

lins, as by the lecithinase of cobra venom.

**LYSOGENIC STRAINS**

See Bacteriophage.

**LYSOZYME**

A bacteriolytic substance found in tears and also in tissues, a yellow amorphous powder soluble in water and containing no nitrogen, phosphorus or sulfur. It is a colloid and its lytic activity varies with the acidity and type of bacteria.

See Eye, Biochemistry of.

**LYXOSE**

C<sub>5</sub>H<sub>10</sub>O<sub>5</sub>; an aldopentose with the configuration of the  $\gamma$ -carbon opposite that of the  $\alpha$ - and  $\beta$ -carbons. It does not occur naturally but is prepared by the degradation of galactonic acid; m.p. 106-107°, showing mutarotation (d-form).

## M

### MACROPHAGE

Large, mononuclear phagocyte; clasmatocyte.

### MAGNESIUM POISONING

See Toxicology.

### MAGNESIUM TEST

See Hahn.

### MAILLARD TEST FOR INDOXYL IN URINE

10 cc. urine are mixed with 1 cc. lead subacetate solution, filtered, and an equal volume of hydrochloric acid added to the filtrate; shaking with chloroform gives rise to a blue color. Shaking with hydrogen peroxide should be performed if no color is obtained.

Reference: Pharm. Zentralhalle 1910, 642.

### MAINTENANCE METABOLISM

Basal metabolism.

### MALACHIN REACTION FOR STRYCHNINE

1 cc. strychnine solution (not more than 0.1% strychnine) is treated with 1 gm. zinc and 1 cc. hydrochloric acid for 2-4 minutes, heated to boiling rapidly, cooled and floated on sulfuric acid. A rose-red ring (sensitivity—1:100000) forms immediately.

Reference: J. pharm. chim. 1909, 546. Bull. sci. pharmacol. 34, 689 (1927).

### MALARIA

A group of fevers caused by mos-

quito-transmitted protozoa (Plasmodia); intermittent fever, remittent fever, ague, tertian fever, quartan fever, estivo-autumnal fever, paludism. The parasite destroys the red blood cells. There are many varieties including masked and latent forms. Quinine and atabrine have been used prophylactically. Quinine, plasmochin and atabrine are administered in short or long treatments.

### MALIC ACID

$C_4H_6O_5$ ; l-hydroxysuccinic acid; l-form occurs in acid fruits such as grapes, apples, gooseberries, and is a product of the fermentation of fumarates by *Aspergillus niger*; m.p.  $100^\circ$ , boils and decomposes at about  $140^\circ$ ; antiseptic against gas bacillus.

### MALIC ENZYME

A pyridinoprotein enzyme which specifically catalyzes the oxidation of l(-)-malate to oxaloacetate; found in heart, brain, kidney, skeletal muscle, liver, blood.

### MALOL, MALOLIC ACID

See Ursolic Acid.

### MALT

Germinated barley grain, heated and dried, contains much maltose; used as a food adjunct.

### MALTA FEVER

See Brucellosis.

### MALTASE

See Enzymes, Non-Proteolytic.

**MALTOSE**

A reducing disaccharide prepared by the enzymatic hydrolysis of starch. It is glucopyranose-4- $\alpha$ -glucopyranoside.

**MALVIN**

A chromo-glucoside from flowers of *Malva silvestris*.

**MAMMARY GLAND, ATROPHY OF**

See Autolysis.

**MAMMATROPIN**

See Prolactin.

**MANDELIC ACID**

Amygdalic acid; paramandelic acid; phenylglycolic acid;  $\alpha$ -phenyl-hydroxy-acetic acid; 1-and d-forms; m.p. 118-119° occurs in glycosides, like amygdalin; used as urinary antiseptic in acid urines.

**MANDELIC ACID THERAPY**

See Urology.

**MANNAN A**

A mannose polysaccharide from ivory nuts consisting of mannopyranose units.

**MANNANS**

Mannosans.

**MANNINOTRIOSE**

Glucose galactose galactoside found in ash manna; m.p. 150°.

**d-MANNITOL**

Manna sugar; d-mannite; a hexahydroxy hexane, obtained by reduction of fructose or mannose. It is found in many plants together with d-sorbitol which is a stereoisomer; m.p. 166-8°; used as a mild laxative and in diabetes.

**MANNOSANS**

Polysaccharides found in plant structures, e.g. ivory nuts. Unlike cellulose they yield mannose on hydrolysis.

**d-MANNOSE**

A hexose derived from mannans; m.p. 132°.

**MANNOTRIOSE**

See Trisaccharides.

**MANUILOFF REAGENTS**

I. 1% alcoholic solution of dahlia or methyl violet.

II. 1% aqueous papayotin solution.

III. 1% potassium permanganate solution.

IV. 2% thiosinamine solution.

V. 40% hydrochloric acid.

These are used in sex determination.

Reference: Münch. med. Wochschr. 71, 1784 (1924). Biochem. Zeit. 176, 189, 198, 251 (1926).

**MANURE**

See Cellulose Decomposition.

**MARBLE BONES**

See Bone, Influence Of Diet On.

**MARÉCHAL TEST FOR BILE PIGMENTS**

The neutral or acid urine solution is treated with 2-3 drops of tincture of iodine. An emerald-green color is obtained, changing after  $\frac{1}{2}$  hour to rose-red and finally to yellow.

Reference: Pharm. Zentralhalle 1868, 362; 1894, 308. J. Med. Sci. 1876, 449. Zeit. anal. Chem. 33, 503; 34, 127, 490. Zentr. inn. Med. 1922, 185. Chim. ind. agr. biol. 12, 110 (1926).

**MARGARIC ACID**

n-heptadecylic acid, a synthetic acid showing no connection with margarine.

**MARIHUANA TEST**

See Viehover.

**MARSH TEST FOR ARSENIC**

The reduction of arsenic in its

compounds by nascent hydrogen produces arsine,  $\text{AsH}_3$ , burning with a blue flame and decomposing on heating to form a mirror of metallic arsenic.

3-5 gm. arsenic-free zinc are placed in a flask connected through a stopper to a glass tube bent horizontally and constricted to a capillary in the middle. 25 cc. of 2% sulfuric acid are placed in the flask and, after 20-30 minutes, the test sample is introduced in to the reaction flask. The tube is gently heated just before the constriction, leading to the deposition of arsenic as a black mirror in the constriction. Although antimony gives a similar mirror, it may be differentiated chemically.

Reference: Edinburgh N. Phil. J. 1836, 229. Ann. 77, 125 (1851). J. pharm. chim. (3), 17, 125. Chem. News 27, 189; 38, 301. Zeit. anorg. Chem. 15, 857 (1902). Am. Acad. Arts. Sci. 26, 24. Helv. Chim. Acta 1918, 475; 1923, 258.

#### MARX-SOBOTKA REAGENT AND REACTION FOR EQUILENIN AND DIHYDROEQUILENIN

Coupling of equilenin with diazotized p-nitrobenzene-azodimethoxyaniline gives rise to a deep blue color; dihydroequilenin gives a brownish-red precipitate on coupling which is soluble in organic solvents with the formation of a blue color.

Reference: J. Biol. Chem. 114, 693 (1938).

#### MASTIGOPHORA

See Protozoa.

#### MATERIA MEDICA

See Pharmacology.

#### MATEZITE

See Pinitol.

#### MATING TYPES

See Genetics.

#### MAY AND ROSE METHOD

A reliable method for determining tryptophan by heating the substance to be tested with  $\text{HCl}$  and para-dimethylamino benzaldehyde, whereupon a blue color forms which can be assayed colorimetrically.

#### MAYER REAGENT FOR DETECTING LEUKOCYTE IN- CREASE IN BLOOD.

When a minimum of about 19000 leukocytes are present in blood, the characteristic guaiac reaction is obtained when the blood is treated with guaiac tincture and turpentine.

Reference: Klin.-therap. Wochschr. 1903, 1267.

#### MEAT, SOFTENING OF

See Autolysis.

#### MECHOLYL

Mecholin, acetyl- $\beta$ -methylcholine chloride;  $(\text{CH}_3)_3\text{N}-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{O}-\text{OCCH}_3$ ; m.p.,  $171-173^\circ$ ; used as parasympathetic stimulant.

#### MECHOLYL CHLORIDE

See Ion Transfer (Therapeutic).

#### MECONIC ACID

An acid from opium,  $\text{C}_7\text{H}_4\text{O}_7 \cdot 3\text{H}_2\text{O}$ , said to be nonpoisonous and having little physiological action.

#### MECONIUM

(1) The fecal matter discharged by the new-born. It is a dark-green substance, consisting of mucus, bile, and epithelial threads. (2) Opium.

#### MEDES TEST FOR ASCORBIC ACID IN URINE

5 cc. of urine are treated with 1 cc. of formaldehyde, 0.5 cc. of buffer solution (100 cc. 2M sodium acetate and 30 cc. 2M acetic acid) and 1 cc. of Folin's uric acid reagent; a blue color is obtained if ascorbic



acid is present. The color may be used in the colorimetric determination of the acid.

Reference: Biochem. J. 29, 2251 (1935). J. Biol. Chem. 106, 311 (1934).

## MEDULLA

The portion of an organ or tissue that resembles bone marrow in appearance.

## MEDULLA OBLONGATA

See Nervous System.

## MEIOSIS (MIOSIS)

(1) Excessive contraction of the pupil. (2) The process in the maturation of the germ cells by which the chromosome number is reduced from diploid to haploid. (3) That stage of disease during which the intensity of the symptoms diminishes.

## MELANIN

(1) The brownish-black pigment of hair, skin and the choroid of the eye, formed by the oxidation of tyrosine by the enzyme tyrosinase. (2) The older, obsolescent name for humin.

See also Hair.

## MELANIN PIGMENTATION, HEREDITARY

See Genetics.

## MELANIN TESTS

See Jaksch, Krauss (in urine).

## MELANOGEN TEST

See Jaksch.

## MELANOPROTEIN

An intensely black chromoprotein with melanin as the prosthetic chromogen which forms the pigment of black wool.

## MELEZITASE

See Enzymes, Non-Proteolytic.

## MELEZITOSE

$C_{18}H_{32}O_{16}$ ; a non-reducing trisac-

charide which occurs in a manna that forms on the Douglas fir and other trees as the result of the activity of a soft scale insect. On hydrolysis with invertase it gives turanose or 3- $\alpha$ -D-glucosyl-D-fructose, and glucose; m.p. of hydrate 153°.

## MELIBIASE

A d-galactoside hydrolyzing enzyme found in bottom yeast, almonds and other plants, that splits melibiose into sucrose and galactose, optimum pH, 5.5.

See Enzymes, Non-Proteolytic.

## MELIBIOSE

$C_{12}H_{22}O_{11}$ ; a reducing disaccharide, 6-( $\alpha$ -galactosyl)-D-glucose, obtained by the hydrolysis of raffinose, a trisaccharide which occurs in beet molasses, with dilute acids or invertase.

## MELICITOSE

See Melezitose.

## MELIN

See Rutin.

## MELISSIC ACID

A saturated fatty acid,  $CH_3(CH_2)_{29}COOH$ , found in beeswax; m.p. 90-91°.

## MELISSYL ALCOHOL

See Myricyl Alcohol.

## MELLITURIA

See Glycosuria.

## MELITURIAS, NON-DIABETIC

See Glycosurias, Non-Diabetic.

## MEMBRANE POTENTIAL

See Protoplasm, Bioelectric Potentials.

## MEMBRANES

See Permeability.

## MEMBRANES, PROTOPLASMIC

See Protoplasm.

## MEMBRANES, SELECTIVE

See Electrolyte Balance in Muscle.

**MENOPAUSE**

See Hypo-Ovarianism.

**MENORRHAGIA**

See Hypermenorrhea.

**p-MENTHADIENE**

A monocyclic terpene of chenopodium oil.

**MENTHOL**

$C_{10}H_{20}O$ ; hexahydrothymol; peppermint camphor; l-form, terpene alcohol found in peppermint oils; m.p. 41-43°, b.p. 212°; isomers have been reported; used as analgesic in liniments and in inhalants.

**MENTHONE**

$C_{10}H_{18}N$ ; terpene aldehyde; l-form found in peppermint, geranium, pennyroyal oils.

**MERCAPTAN TESTS**

See Deniges, Nencki, Rheinboldt.

**MERCAPTURIC ACID**

See Detoxication.

**MERCUROCHROME (SOLUBLE)**

A sodium salt of dibromfluorescein mercury hydroxide; mild antiseptic.

**MERCURY TEST IN URINE**

See Lombardo.

**MERTHIOLATE**

A commercial name for Na ethylmercurithiosalicylate; a powerful germicide which does not precipitate with serum proteins.

**MESAMORPHIC STATE**

See Liquid Crystals.

**MESCALINE**

Mezcaline;  $C_{11}H_{17}O_3N$ ; an alkaloid of mescal buttons, m.p. 35-36°, exhibits narcotic-tetanic effects and is probably responsible for the color visions of mescal poisoning.

**MESEMBRINE**

An alkaloid from mescal buttons exhibiting narcotic-tetanic properties.

**MESO-COMPOUNDS**

These compounds have an even number of asymmetric carbons, the members of any pair having a rotation tendency equal to each other, but opposite in sign, so that the total effect is of no optical activity.

**MESONEPHROS**

See Wolffian Body.

**MESOZOIC ERA**

Era of reptiles; includes the cretaceous, the jurassic and triassic.

**METABOLIC BODY SIZE**

Size of animals expressed in terms of metabolic rate, such as Calsads (see this), similar to horsepowers as index for size of motors. Metabolic body size may also be expressed in terms of functions to which the metabolic rate is proportional such as body surface or, more recently, the  $\frac{3}{4}$  power of body weight. M. K.

**METABOLISM**

Sum of all chemical changes in an organism. Includes anabolism and catabolism (see this). Attention may be focussed on particular aspects: Mineral-carbon, nitrogen, energy-metabolism. M. K.

**METABOLISM AND ELECTROLYTES**

See Electrolyte Balance in Muscle.

**METABOLITE**

Any substance produced by metabolism.

**METABOLIZABLE ENERGY**

Physiological fuel value of food. Energy, which is available for all metabolic processes in animal body. Heat of combustion of food minus heat of combustion of feces, urine and methane.

M. K.

## METAGENESIS

The alternation of a generation which reproduces only asexually by division or budding with a generation which reproduces only sexually by means of eggs and spermatozoa.

## METAPHEN

A commercial name for the anhydride of 4-nitro-5-hydroxymethylmercuri-o-cresol, a very powerful germicide, used in urogenital infections.

## METAPLASIA

The change of one kind of tissue into another; also, the production of tissue by cells which normally produce tissue of another sort.

## METAPLASM

Alloplasm; paraplast; deutoplasm; lifeless material in protoplasm.

## METAPROTEINS

(1) The American classification of proteins places it in the second group of the hydrolysis products of proteins, being classified just after the proteins. They are insoluble in neutral solvents, but soluble in weak acids and alkalis.  
(2) First stages in protein degradation, soluble in dilute acids and alkalis but not in water or salts.

## METAZOA

Many-celled animals.

## METHEMOGLOBIN

A compound formed from oxyhemoglobin or red hemoglobin by mild oxidation. It has the Fe in the ferric state, unlike oxy- or reduced hemoglobin.

See Hemoglobin.

## METHENAMINE TEST

See Labat.

## 1-METHIONINE

$C_5H_{11}O_2NS$ ; alpha-amino-gamma-methylmercapto-butyric acid; m.p.  $283^\circ$ ; naturally occurring form is levorotatory; a sulfur containing amino acid present in hydrolytic products of many proteins, which is indispensable for metabolism. See also Hair.

## METHIONINE METABOLISM

Methionine is an almost ubiquitous protein constituent. It is an essential component of mammalian diet because the capacity for synthesizing this amino acid from inorganic matter seems to be confined to plant life. Its methyl ( $CH_3$ ) group can participate in the biosynthesis of choline, creatine, and related substances from methionine by a mechanism which is still unknown. Ingestion of excessive amounts of methionine results in excretion of urinary sulfates.

## METHYLAMINE TEST

See Valton.

## METHYLCHOLANTHRENE

$C_{21}H_{16}$ , a cancer-producing yellow hydrocarbon prepared from cholic acid, m.p.  $177^\circ$ .

See Carcinogenetic Hydrocarbons.

## 5-METHYLCYSTOSINE

A pyrimidine derivative found in the nucleic acids.

## METHYL GLYOXAL

See Pyruvic Aldehyde.

## METHYLGLYOXAL TEST

See Denigès.

## METHYL GUANIDINE

See Creatine and Creatinine Metabolism.

## METHYLGUANIDINE TEST

See Pfiffner-Myers.

**METHYLIMIDAZOLE TEST**

See Koessler-Hanke.

**METHYLTHEOBROMINE**

See Caffeine.

**METHYLTHIOPENTOSIDES**

Nucleosides containing sulfur, as adenine methylthiopentose of yeast.

**METRAZOL**

Cardiazol;  $C_6H_{10}N_4$ ; m.p. 57-58°; a commercial name of pentamethylenetetrazol, a vasomotor and respiratory stimulant. See Pharmacology.

**METRAZOL IN MENTAL DISEASE**

See Psychiatry, Biochemistry of.

**METRAZOL TEST**

See Zwikker.

**METRORRHAGIA**

See Polymenorrhea.

**MEYERHOF QUOTIENT**

M.Q.; a measure of the resynthesis of glucose or the amount of lactic acid reconverted to glucose per unit oxygen consumption.

**MICELLE**

A particle of the dispersed phase in a colloidal system.

See Protoplasm.

**MICHEL REAGENT FOR DIFFERENTIATING OXYHEMOGLOBIN AND CO-HEMOGLOBIN**

Reagent prepared by dissolving 4 gm. potassium hydroxide in 75 cc. water and adding 3 gm. sodium hydrosulfite ( $Na_2S_2O_4$ ). After solution is complete, 40 cc of 98% alcohol are added and the solution filtered; it must be kept out of contact with air.

Reference: Chem.-Ztg. 1911, 996.

**MICRO-AEROTONOMETER**

An instrument for equilibrating a minute bubble of air with blood and analyzing the absorption (Krogh).

**MICROBIOLOGY**

The subject of microbiology deals with microscopic or even sub-microscopic organisms, variously known as microbes, microorganisms or germs. These may be plants, animals or of an uncertain classification. Divisions of the subject follow the classifications of organisms, e.g. mycology deals with molds, protozoology with protozoa and bacteriology with bacteria. The divisions are not absolutely sharp, so that a subject like bacteriology may deal with viruses and rickettsia and selected groups of molds, yeasts and protozoa. A classification suggested by Birkeland is general bacteriology, soil bacteriology, dairy bacteriology, food bacteriology, industrial bacteriology, sanitary bacteriology, veterinary bacteriology, medical bacteriology, immunology and serology. Neighboring fields are many, e.g. epidemiology and public health science.

Bacteria and unicellular animals are classified often by biochemical activity, staining and chemical composition as well as disease-producing power, morphology and general biological characteristics. The biological phylum thallophyta (plants without roots, stems, leaves) contains the sub-phyla, algae (chlorophyll-containing) and fungi, which include yeasts, molds and bacteria. The fungi fall into the following classes: (1) Schizomycetes (fission fungi, bacteria) (2) Saccharomycetes (yeasts) (3) Phycomycetes (forms without cross walls between cells) (4) Ascomycetes (forming spores in a sac) and (5) Basidiomy-

cetes, forms in which sexual stages are unknown, and slime molds.

The Schizomycetes or bacteria are usually described as cocci (spheres), bacilli (rods) and spirilla (spirals). The streptococci appear as chain-like beads. The staphylococci appear in irregular clusters. Some spirilla look like a comma, e.g. the comma or vibrio bacillus. Many bacteria form spores and are surrounded by capsules of protein or carbohydrate nature. Classifications are far from complete. Seven or eight orders of Schizomycetes are listed: (1) Eubacteriales, true bacteria; (2) Actinomycetales, mold-like bacteria; (3) Chlamydobacteriales, sheathed bacteria (4) Caulobacteriales, stalk bacteria; (5) Thiobacteriales, sulfur bacteria; (6) Myxobacteriales, slime bacteria; (7) Spirochaetales, protozoan-like bacteria (8) Rickettsia, (?). The orders are divided into numerous families, and these successively into various tribes, genera and species.

Yeasts are often described as true and false, distinguished as to whether they bud by forming endospores or not. The true yeasts include many kinds of Saccharomyces. Practical brewers use convenient designations as top yeasts and bottom yeast which differ in the vigor of fermentation. Wild yeasts are called torula, which frequently produce strong pigments. There are numerous sub-groups classified by fermentation characteristics.

Molds are fungi commonly associated with decay and food spoilage. Common types are Phycomycetes and Ascomycetes (sac-molds). The former contain the family Mucoraceae and its genera Rhizopus and Mucor, commonly referred to as

bread molds. Among the Ascomycetes are the well known *Aspergillus niger* and the *Penicillium* (meaning brush-like). The flavors of cheeses are often due to *Penicillia*.

Microbiology is concerned with not only the morphology but the physiology of microorganisms. Bacterial metabolism, growth and participation in the cycles of nature are important fields of study. The production of enzymes by bacteria ranks as a science in itself and is used as a basis for differentiating them. The feeding characteristics of bacteria lead to their designation as autotrophic (self subsistent on simple inorganic compounds) or heterotrophic (requiring some built up organic substances as well). The metabolism is described as fermentation, with stress on incomplete carbohydrate breakdown, or putrefaction, with stress on incomplete protein breakdown. Both fermentation and putrefaction come under the term dissimilation, which is the opposite of assimilation. Microbial attack of cellulose, hemicellulose, pectin, lignin, starches, gums, sugars, waxes, etc., has been studied for a great variety of conditions, and the findings help to explain the carbon cycle in nature. Similarly the nitrogen cycle depends on its explanation at least at two points, namely nitrification and nitrogen fixation in the soil and protein decomposition and putrefaction. The autotrophic *Nitrosomonas* converts ammonia to nitrous acid. Nitrogen fixers are symbiotic and free living. Among the former are the genera *Rhizobium* and *Mycobacterium*, and among the latter is the aerobe, *Azotobacter chroococcum*, and the anaerobe, *Clostridium butyricum*. Very many bacteria are proteolytic.

Besides carbon and nitrogen the natural history of sulfur compounds, potassium, phosphorus and calcium includes the activity of bacteria.

The genetic history and possibilities of bacteria are included in this field. Moreover, environmental influences, such as temperature, radiation, pressure, moisture, light, etc., have been studied in great detail. The effect of chemical agents has been of particular importance in the development of antiseptics (bacteriostatic substances), preservatives, disinfectants (germicides, fungicides, bacteriocides) and deodorants (putrefaction inhibitors). The so-called phenol coefficient is a measure of sterilizing power against bacteria.

The field of study of infection is intimately allied to microbiology. The manner of invasion of bodies by microorganisms and their own struggle for survival or for symbiosis constitute branches of the subject. The production of harmful or beneficial substances belongs to biochemistry rather directly. Thus bacteria may produce hemolysins, which are substances which break down red blood cells and are species specific; leucocidins, or substances which destroy white blood cells and are species specific; coagulases and fibrinolysins which cause formation of blood clots or their solution; "spreading factor," a substance which affects the permeability of tissue (also known as Duran-Reynolds factor); and toxins or poisons secreted by bacteria; roughly classified as exotoxins definitely found diffusing from the bacterial cell and endotoxins which are liberated when the bacterial cell is disrupted.

The defense of the body against

the invasion of bacteria and their toxic substances leads to the entire field of immunology (q.v.). The spreading of infection when it becomes a mass phenomenon is known as epidemiology. The number of diseases is not large compared to the great variety of organisms, of which few are relatively harmful, but it runs to quite a list. Thus staphylococci might cause septicaemia, pyemia, boils, pimples, abscesses, impetigo, osteomyelitis. Streptococci, such as *Streptococcus viridans*, are credited with teeth abscesses, rheumatic fever, arthritis, sinus infections and sub-acute bacterial endocarditis. *Streptococcus hemolyticus* is credited with erysipelas, scarlet fever, septic sore throat, tonsillitis, bronchopneumonia, middle ear infection, puerperal sepsis. A large chapter can be written on the several types of pneumonia produced by pneumococci. For whooping cough one must study *Hemophilus pertussis*; for diphtheria, *Corynebacterium diphtheriae* or the Klebs-Loeffler bacillus; for tuberculosis, *Mycobacterium tuberculosis* or the tubercle bacillus; for leprosy, *Mycobacterium leprae*. The same general state of affairs is true for dysentery, typhoid fever, cholera, plague, tularemia, brucellosis or undulant fever, rickettsial diseases (typhus and Rocky Mountain spotted fever), syphilis, gonorrhea, etc., etc. In some cases viruses are no doubt responsible, e.g. the common cold, measles, mumps, poliomyelitis (infantile paralysis), some forms of encephalitis, rabies, psittacosis (parrot disease), smallpox, yellow fever.

Applied microbiology is not only concerned with medicine but also with food. Food spoilage, preserva-



tion and processing depend on microorganism control. Water purity and milk purity are equally vital microbial control problems. Sewage disposal is a vast field of problems involving detailed microbiological knowledge. These are more important than spectacular poisonings due to decomposing food, such as botulism due to *Clostridium botulinum*, and several other similar types.

In the study of microorganisms in the soil, furthermore, not only is material found of interest to agriculturalists but also to engineers, because indirectly the strength of structures, highways, airports, etc., is dependent on microbiological facts.

W. M. M.

References: Microbiology and Man, J. Birkeland. Crofts, 1942.

#### MICROCIONASTEROL

An animal sterol of the sponge, *Microciona prolifera*, containing one double bond.

#### MICROCYTE

See Hematoblast.

#### MICRODISSECTION

See Protoplasm.

#### MICROINCINERATION

See Histochemistry.

#### MICROMANIPULATION

See Protoplasm.

#### MICRONS

(1) 0.001 mm.

(2) In the Siedentopf and Zsigmondy classification of particle size, those particles visible in the microscope.

#### MICRONUCLEUS

See Protoplasm.

#### MICROSCOPIC VISIBILITY

See Protoplasm.

#### MICROSCOPY, DARK-FIELD

See Protoplasm.

#### MICROSCOPY, ULTRAVIOLET

See Protoplasm.

#### MICRURGY

See Protoplasm.

#### MIDBRAIN

See Nervous System.

#### MIGRAINE

See Ergot.

#### MILDEW

See Cellulose Decomposition.

#### MILIEU INTERIEUR

Body fluids of an organism; the "internal environment."

#### MILK

The white aqueous secretion of the mammary glands, pH 6.6-6.9, which is the sole source of nourishment of the young mammal. It contains 90% water, proteins, mostly casein, fat, mostly glycerides of the higher fatty acids, lactose, minerals, vitamins, particularly A & G, and other constituents. Normal volume in humans varies from 1500 cc. to somewhat more than 3000 cc. at any one time.

#### MILK FLAVOPROTEIN

See Xanthine Oxidase.

#### MILK PRODUCTION

See Agricultural Biochemistry.

#### MILK SUGAR

Lactose.

#### MILLON REAGENT FOR PROTEINS

Reagent—1.1 solution of mercury in fuming nitric acid diluted with 2 volumes of water. A brick-red precipitate is obtained when a protein is heated with the reagent. Reference: Compt. rend. 28, 40 (1849). Pharm. Prax. 1880, 11, 142.

**MINKOWSKI TEST FOR HYDROXYBUTYRIC ACID IN URINE**

The urine is evaporated, the residue extracted with alcohol, the solvent evaporated and the residue is dissolved in water. The solution is acidified with sulfuric acid, extracted with ether, the solvent is evaporated, the residue dissolved in alcohol and purified with animal charcoal. After neutralization with sodium hydroxide, the solution is evaporated to a syrup. On addition of a few drops of a saturated silver nitrate solution a magma of finely felted needles is obtained.

Reference: Arch. exptl. Path. Pharmakol. 18, 35, 147. Zeit. Biol. 20, 157.

**MITOGENETIC RADIATION**

Feeble ultraviolet radiation emitted by developing cells which can increase mitosis, or the rate of cell division; also known as Gurvitch rays; many doubt their very existence.

**MITOSIS**

See Wound Healing.

**MITRAGYNINE**

An alkaloid,  $C_{17}H_{22}N(OCH_3)(COOCH_3)_2$ , from the leaves of *Mitragyne speciosa*, and possessing local anesthetic properties.

**MNEMODERMIA**

See Itching.

**MODULATORS**

Substances responsible along with evocators and organizers for regional determination of developing cells.

**MOLAR GAS CONSTANT**

The constant  $R$ , in the General Gas law;  $PV=nRT$ , where  $P$ =pressure,  $V$ =volume,  $n$ =number of moles and  $T$ =Temp in °A. It

is equal to 0.08204 liter-atmospheres.

**MOLDS**

See Microbiology.

**MOLD, SLIME**

See Protoplasm.

**MOLD, SLIME, COMPOSITION OF**

See Protoplasm.

**MOLECULAR WEIGHTS OF PROTEINS**

See Protein Structure.

**MOLISCH TEST**

A specific test for carbohydrates.  $\alpha$ -naphthol is added to the solution to be tested, and stratified over concentrated sulfuric acid. A pink to red color is positive.

**MOLISCH TEST FOR ALBUMIN**

1 cc. of test solution is treated with 2 drops of a solution of 20 gm. naphthol in 100 gm. alcohol and 5 cc. of concentrated sulfuric acid; a red or violet color is obtained if albumin or peptone is present.

Reference: Monatsh. 7, 198 (1887).

**MOLLUSCA**

These include: Lamellibranchiata—mussels, clams, scallops; Gastropoda—snails, winkles, slugs; Cephalopoda—cuttlefishes, squids, octopus.

**MONARDIN**

See Pelargonin.

**MONONUCLEOTIDES**

The constituent parts of the nucleic acids, containing one molecule of either a purine or a pyrimidine derivative, a carbohydrate and a phosphoric acid molecule. The phosphoric acid is esterified with  $C_2$  or  $C_5$  of the sugar, which

in turn is connected to a N of the purine or pyrimidine.

4 nucleotides go into making a nucleic acid molecule. See Guanylic acid.

#### MONOPHENOL OXIDASE

A mushroom copper protein which catalyzes the oxidation of monophenols to their quinones, but can also attack polyphenols more slowly.

#### MONOSE

Formaldehyde. For purposes of analogy it is classified with the monosaccharides, but it is not a carbohydrate.

#### MONTANIC ACID

A 28 carbon saturated fatty acid found in Montan wax.

#### MONTIGNIE REACTION FOR STEROLS

A red-brown color is obtained when an alcoholic solution of a sterol is gently heated with silicotungstic acid. Cholesterol, ergosterol, phytosterol and stigmasterol give the reaction; only a faint reddish-yellow color is given by  $\alpha$ - and  $\beta$ -cholesterylenes and cholestenone.

Reference: Bull. soc. chim. 51, 690 (1932).

#### MONTIGNIE TEST FOR ERGOSTEROL AND ITS DERIVATIVES

A solution of the substance in 5 cc. of alcohol is heated to 95° and treated with 3-4 cc. of a 10% selenious oxide solution; a red precipitate developing within 2 minutes indicates ergosterol. Cholesterol, phytosterol and stigmasterol do not react.

Reference: Bull. soc. chim. 51, 144 (1932).

#### MONTIGNIE TEST FOR INDOLE, PYRROLE AND SKATOLE

The aqueous solution of the substance is heated with 8-10 drops of 10% selenious acid solution and 1 cc. nitric acid. A violet color, sensitivity—0.04 mg., is given by indole. Pyrrole forms a blue substance soluble in chloroform and a red chloroform-insoluble substance, sensitivity—0.4 mg. A red solution is given by skatole but, in the absence of nitric acid, a violet color, changing to red with nitric acid, is obtained.

Reference: Bull. soc. chim. 51, 689 (1932).

#### MOORE'S TEST

A test for sugars, depending on the decomposition of the sugar when boiled in alkalis, giving a brown color and an odor of caramel.

#### MOOR URINE OR UREA REACTION

5 drops concentrated ammonia and 0.1-0.2 gm. solid phosphotungstic acid are added to 5 cc. of urine which becomes an intense blue immediately. A weak reaction is obtained where metabolism is impaired or where kidney function is impaired.

Reference: Biochem. Zeit. 149, 575 (1924).

#### MOREL-MARTHOUX REACTION

See Digitalis.

#### MORIN

3,5,7,2',4',-pentahydroxyflavone; the coloring matter of the wood of old fustic, m.p. 285°, a sensitive reagent for aluminum.

#### MORINDIN

A glucoside,  $C_{28}H_{28}O_{14}$ , from root bark of Morinda citrifolia; m.p., 250-251°.

**MÖRNER TEST FOR ACETOACETIC ACID IN URINE**

A strong odor of iodo-acetone, strongly irritating to the mucosa, is obtained when the urine is boiled with an excess of potassium iodide and ferric chloride. The odor is easily distinguished from iodine odor.

Reference: Zeit. anal. Chem. 35, 637 (1896).

**MÖRNER TEST FOR CYSTEINE**

The addition of an alkali and sodium nitroprusside to a cysteine solution gives rise to a persistent purple-red color. The color is due to the presence of the sulfide group in the substance.

Reference: Zeit. physiol. Chem. 28, 611 (1899); 49, 397 (1906). Chem.-Ztg. 1910, 333.

**MORPHINE**

$C_{17}H_{19}O_3N$ ; prisms with one  $H_2O$ ; anhyd. m.p.  $254^\circ$ ; a strongly habit-forming analgesic alkaloid of opium. Exerts a simultaneous depressing and exciting effect on the central nervous system. Causes respiratory depression and death. See Toxicology.

**MORPHINE TEST**

See Aloy-Valdiguie.

**MORPHINESTERASE**

See Enzymes, Non-Proteolytic.

**MORPHOLOGY**

The study of form and structures.

**MORULA**

The segmented ovum in the mulberry stage, forming a solid mass of cells.

**MOSS STARCH**

See Lichenin.

**M.Q.**

See Meyerhof Quotient.

**MOTT-HALIBURTON TEST FOR CHOLINE**

Choline forms a double crystalline compound with platinum chloride. Reference: Phil. Trans. Roy. Soc. London 1899, 199, 218.

**MOULTING**

See Hair.

**MOUSE UNIT OF ESTROGENIC ACTIVITY**

The least amount of estrus-producing hormone (estrone) which will cause in a spayed mouse a characteristic degeneration of the vaginal epithelium (averaged over several animals in a given colony.)

**MUCIC ACID**

$COOH(CHOH)_4COOH$ ; tetrahydroxy-adipic acid; saccharolactic acid; an oxidation product of galactose; m.p.  $255^\circ$  with decomposition.

**MUCIC ACID TEST**

See Glycosurias, Non-Diabetic.

**MUCILAGES**

Salts, either with metals or organic bases, of polysaccharide sulfuric acid esters, which gel with water. Galactose is probably at least a part of the carbohydrate part of the compound.

Examples: agar-agar and carrageen.

**MUCINS**

A group of glycoproteins occurring in or made by glands, e.g. submaxillary gland and liver, containing a high percentage of carbohydrates; particularly mucosin sulfuric acid. The mucins form very hydrophilic colloids.

**MUCOIDS**

A group of conjugated glycoproteins where the protein is conjugated with chondroitin sulfuric

acid. They are viscous bodies found in tendons, cartilage, etc.

### MUCOITIN SULFURIC ACID

One of the two carbohydrate groups associated with the protein of the glycoproteins. It consists of 2 molecules of mucosin (amino glucose) with one hydroxyl esterified with sulfuric acid and the amino groups acetylated. Each of these mucosin molecules is linked to a molecule of glucuronic acid, which in turn are connected to each other.

### MUCONIC ACID

See Detoxication.

### MUCOR

See Microbiology.

### MUCUS

A condensation product of monoses produced by bacterial action, variously described as a starch, a cellulose or an anhydride of glucose called "dextran" or an anhydride of fructose called "levan."

### MULTIPAROUS

Giving birth to more than one at a time.

### MULTIPLE ALTERNATE OXIDATION THEORY

A modification of the  $\beta$ -oxidation theory of Knoop, advanced by Jowett and Quastel. Oxidation of fatty acids take place simultaneously along the entire molecule, at the  $\beta$ ,  $\delta$ ,  $\zeta$  even-numbered carbons, preceded by desaturation of the molecule.

See Fat Metabolism.

### MUMPS

Epidemic parotitis; acute contagious infection of parotid gland which may affect the gonads, the pancreas and other glands and the central nervous system, mani-

fested by swelling and fever. Testicular atrophy or deafness may follow.

### MUNJISTIN

A glycoside of 2:4-dihydroxy-anthraquinone-3-carboxylic acid from roots of *Rubia munjista*; m.p. 229-230°.

### MUREXIDE REACTION

The murexide reaction depends upon the formation of the deep violet ammonium salt of purpuric acid from uric acid and related purines. 2-3 drops of concentrated nitric acid are added to a small amount of the substance in a porcelain dish and the solution carefully evaporated to dryness. The red or yellow residue, after cooling, turns purplish-red on the addition of a drop of dilute ammonia. The use of potassium hydroxide gives rise to a purplish-violet color.

Reference: Phil. Trans. Roy. Soc. London 1818, 420. Liebig Ann. 26, 319 (1838); 123, 363 (1862); 107, 176 (1858). Ann chim. phys. 28, 289 (1893). Schweiz. Wochschr. Chem. Pharm. 1913, 492. Deut. Med. Wochschr. 1911. 1112.

### MUSCARINE

$(\text{CH}_3)_3 \cdot \text{N}(\text{OH}) \cdot \text{CH}(\text{CHO}) \cdot \text{CHOH} \cdot \text{CH}_2 \cdot \text{CH}_3$ ; according to the older literature, an oxidation product of choline, but later shown to be a higher homologue of this oxidation product. A poison found in certain mushrooms, "fly fungus."

### MUSCLE, DISUSE ATROPHY OF

See Autolysis.

### MUSCLE, ELECTROLYTE BALANCE IN

See Electrolyte Balance in Muscle.

**MUSCLE HEMOGLOBIN**

See Myoglobin.

**MUSCLE PULP RESPIRATION**

See Creatine and Creatinine Metabolism.

**MUSCULAMINE**

See Spermine.

**MUSCULAR CONTRACTION**

See Creatine and Creatinine Metabolism.

**MUSCULAR EXERCISE**

See Creatine and Creatinine Metabolism.

**MUSTARD GAS**

Dichlorethyl sulfide; burns resemble X-ray and drug dermatitis; slow healing and periodic recurrence like the course of an infectious disease.

**MUSTARD GAS TEST**

See Jelinek.

**MUTANT**

A sport or variation which breeds true.

**MUTAROTATION**

The change in rotation observed when a solution of an aldose or ketose is allowed to stand. The exact mechanism is not known with certainty, but it involves changes of one form to a different optical isomer.

**MUTASE**

Oxyreducase; enzyme system which promotes the oxidation of one molecule of its substrate by the reduction of another molecule of the same substrate.

**MYASTHENIA GRAVIS**

A metabolic disease of the muscles possibly brought on by infection, showing as marked weakness. There is an increase of creatine and a decrease of creatinine in the urine. Prostigmine relieves

symptoms. Glycocoll with ephedrine has been used on the supposition of a connection with a disturbance of creatine metabolism.

**MYCOLOGY**

See Microbiology.

**MYELOPATHIC ALBUMOSE TEST, IN URINE**

See Bradshaw.

**MYERS-WARDELL TEST FOR CHOLESTEROL**

The blood, after drying on plaster of paris, is extracted with chloroform; the cholesterol is determined colorimetrically after adding acetic anhydride and sulfuric acid to the extract.

Reference: J. Biol. Chem. 36, 147 (1918).

**MYLLUS REACTION FOR CHOLIC ACID**

A solution of 20 mg. cholic acid in 0.5 cc. alcohol is treated with 1 cc. 0.1N iodine and diluted gradually with water. Yellow crystals having a metallic luster and blue by transmitted light are precipitated. Choleic, conjugated bile and hyocholic acids do not give the reaction.

Reference: Ber. 20, 683 (1887). Bull. soc. chim. 1913, 866.

**MYOALBUMIN**

An intracellular water soluble albumin, found in muscle to the extent of about 1% of the total protein; i.p. 3.3.

**MYOCARDIUM, BIOCHEMISTRY OF**

In 1927, Fiske and Subbarow isolated phosphocreatine in the human myocardium and with the later discovery of adenosinetriphosphate our conceptions regarding the energetics of muscular activity underwent considerable clarification.



It became apparent that compounds of phosphorus, phosphocreatine and adenosinetriphosphate in particular, are intermediaries in the transfer of chemical energy to the mechanical energy of the heart beat. These organic phosphoric acid compounds exist as potassium salts and this accounts for most of the intracellular potassium. It is now apparent that the concentration of these compounds in the myocardium serves as an index of the potential energy of the heart for work.

Creatine is present in heart muscle in about half the concentration it attains in skeletal muscle. Phosphocreatine is present in concentrations from one-tenth to one-third that of skeletal muscle. Its lower concentration in heart muscle than in skeletal muscle cannot be attributed to a difference in the amount of the intracellular phase, since there is a sharp decrease in the ratio of creatine to phosphorus. The distribution of phosphorus compounds is likewise greatly different from that of skeletal muscle. While the total phosphorus of the heart is about the same as that of skeletal muscle, a much greater part is present in the acid insoluble fraction, most of which is phospholipid. The acid-soluble fraction is accordingly less, and this difference may be traced largely to the lower phosphocreatine content of the heart.

There is good evidence, direct and circumstantial, that phosphocreatine and adenosinetriphosphate, as potassium salts, play an essential role in muscular activity, or more specifically are vital agents in the transfer of chemical to mechanical energy for muscular work.

EDWARD PODOLSKY, M.D.

#### MYOCHROME

See Myoglobin.

#### MYOGEN

An intracellular water soluble protein; i.p. 6.7.

See also Enzymes, Non-Proteolytic.

#### MYOGLOBIN (MYOCHROME, MUSCLE HEMOGLOBIN)

A hemoglobin found in the fibres of striated muscle. The protein component differs from blood globin, the prosthetic group is the same. The mol. wt. is only 16,500 or one quarter that of hemoglobin. It also differs from the latter with regard to the position of the absorption bands and the affinity to oxygen.

#### MYOHEMOGLOBIN

An iron containing porphyrin of the muscle closely resembling hemoglobin. Iron content is the same but molecular weight (35,000), absorption spectrum, and i.p. (6.99) are different.

#### MYOKININ

A betaine corresponding to arginine found in muscles.

#### MYOPATHY, HUMAN

See Creatine and Creatinine Metabolism.

#### MYOSIN

The most abundant intracellular globulin of muscle (50 to 70% of total protein), insol. H<sub>2</sub>O, sol. dil. salt solutions, i.p. 5.5. Hydrates to form gels. Shows double refraction.

See also Electrolyte Balance in Muscle.

#### MYOSIN, ACID

See Syntonin.

#### MYOSMINE

C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>; 2-(3'-pyridyl)-4,5dihydropyrrol; an alkaloid of tobacco smoke, m.p. 42-43° (vac.).

**MYRCENE**

$C_{10}H_{16}$ ; an acyclic monoterpene, found in oil of hops, verbena, etc.; b.p. 166-168°.

**MYRICYL ALCOHOL**

$CH_3(CH_2)_{29}CH_2OH$ , m.p. 87°, present in beeswax as the palmitate.

**MYRISTIC ACID**

A saturated fatty acid  $CH_3(CH_2)_{12}COOH$ , found in nutmeg butter; m.p. 57-58° C.

**MYRISTOLEIC ACID**

Unsaturated fatty acid,  $C_{18}H_{30}O_2$ , containing one double bond, found in cod liver and whale oils.

**MYROSIN**

A sulfatase present in mustard

seeds which hydrolyses its glycosides; also present in animal tissues.

**MYROSINASE**

See Enzymes, Non-Proteolytic.

**MYRTENOL**

An alcohol derived from pinene found in myrtle oil.

**MYRTICOLORIN**

See Rutin.

**MYTILITOL**

$C_7H_{14}O_6$ ; probably a methyl ether of inositol found in valve muscles of *Mytilus edulis*.

**MYXOBACTERIALES**

See Microbiology.

## N

### NADI REAGENT

Mixture of dimethyl-p-phenylene diamine and alpha naphthol used as a test for indophenol oxidase.

### NAIMAN REAGENT FOR VITAMIN B<sub>1</sub>

Vitamin B<sub>1</sub> gives an orange-red precipitate with potassium-bismuth iodide; the weight of the precipitate is proportional to the vitamin content.

Reference: Science 85, 290 (1937).

### NAPHTHACENE

A yellow hydrocarbon found in small amounts with chrysene. It is a linear benzologue of anthracene.

### NAPHTHALENE-1-ACETIC ACID

See Plant Growth Hormones.

### NAPHTHENE DERIVATIVES, ESTROGENIC ACTIVITIES OF

See Estrogens, Synthetic.

### NAPHTHOLS, TEST FOR

See Alvarez.

### NARCOLEPSY

See Epilepsy.

### NARCOSINE

See Narcotine.

### NARCOSIS

A condition of profound stupor brought about by narcotic drugs.

### NARCOTINE

C<sub>22</sub>H<sub>23</sub>O<sub>7</sub>N; needles, m.p. 176°; opianin; opian; narcosine; alkaloid of opium, 3-18%, a benzyl isoquinoline derivative. Slightly poisonous. Paralyzes smooth muscles. Simultaneously excites and depresses central nervous system; antineuralgic, antispasmodic and antiperiodic; has been used for malaria and migraine.

### NASSE REACTION

A specific test for tyrosine. Heat the material to be tested with an aqueous solution of mercuric acetate or sulfate and a few drops of a 1% solution of sodium nitrate. Tyrosine gives a cherry-red color, tryptophane gives no color.

### NECROHORMONES

See Wound Healing.

### NECROSIS, TRAUMATIC

See Wound Healing.

### NEGATIVE ADSORPTION

See Adsorption.

### NEGATIVE NITROGEN BALANCE

See Nitrogen Balance.

### NEMBUTAL

Pentobarbital-sodium; Na salt of ethyl-alpha-methylbutyl barbituric acid; a popular hypnotic.

**NENCKI-SIEBER TEST FOR UROBILIN IN URINE**

20 cc. of urine are shaken with 10 cc. amyl alcohol and treated with a few drops of 1% ammoniacal alcoholic solution of zinc chloride. The presence of urobilin is indicated by a green fluorescence and a characteristic absorption spectrum.

Reference: J. prakt. Chem. (2), 26, 236 (1882). Boll. chim.-farm. 36, 69 (1897). Chem.-Ztg. 1900. Rep. 211.

**NENCKI TEST FOR MERCAPTAN IN URINE**

The gas evolved from the distillation of urine with oxalic acid is led through mercuric cyanide solution. The resulting precipitate is distilled with hydrochloric acid and the distillate passed into lead acetate solution forming a yellow crystalline precipitate.

Reference: Analyse der Harn 1898, 51.

**NEOARSPHENAMINE**

Neosalvarsan; Na 3-diamino-4-dihydroxy-arsenobenzene-methanalsulfoxylate; a powerful spirillicide used in syphilis, yaws, relapsing fever, malaria.

**NEOARSPHENAMINE TESTS**

See Abelin, Scheringa.

**NEOPINE**

$C_{18}H_{21}O_3$ , needles, m.p.  $127^\circ$ ; an alkaloid of opium, isomeric with codeine. The hydrobromide crystallizes as prisms, m.p.  $282-283^\circ$ .

**NEOSALVARSAN**

See Neoarsphenamine.

**NEOSYNTHALIN**

See Insulin.

**NEPHELOMETRY**

The measurement of the concen-

tration of dispersed particles, based on the measurement of the intensity of the Tyndall cone.

**NEPHRECTOMY**

See Creatine and Creatinine Metabolism.

**NEPHRITIS**

See Creatine, and Creatinine Metabolism, Bright's Disease.

**NEPHROSCLEROSIS**

See Bright's Disease.

**NEPHROSIS**

See Bright's Disease.

**NEROL**

A terpene alcohol present in neroli, petit-grain and bergamot oils, resembles geraniol.

**NEROLIDOL**

A sesquiterpene alcohol found in neroli oil and Peru balsam.

**NERVE IMPULSE**

See Bioelectric Potentials.

**NERVONE**

m.p.  $180^\circ$ ; a cerebroside, whose fatty acid is nervonic acid.

**NERVONIC ACID**

$C_{24}H_{46}O_2$ ; cis-14-tetracosanic acid; an acid found associated with the sphingomyelins and in the cerebroside nervon,  $CH_3(CH_2)_7CH=CH(CH_2)_{13}COOH$ .

**NERVOUS SYSTEM**

Living organisms maintain themselves in an equilibrium state which slowly shifts with time (growth, etc.). But from moment to moment they are called upon to react to environmental changes which act upon them. The external event constitutes a stimulus, usually one involving but little energy, which evokes from the organism some active response, commonly involving much more energy than was in

the stimulus. This sequence involves, therefore, amplification or "trigger action" by the organism; and, further, the energy released is not squandered but is directed to certain uses. The response is such as to counteract the stimulus, to maintain the equilibrium status, and so to adapt the organism. Such "adaptive amplification" is a universal property of organisms.

Protoplasm itself is irritable, it responds to stimuli, but inefficiently and sluggishly. Relatively strong stimuli are required to disturb it, the excitation finally set up does not spread far or fast from the stimulated region, and the response is slow and inexpert. The slow formation of a pseudopod by an amoeba, on the surface opposite a portion poked with a needle, is a fair example; the drooping of a burned leaf of the sensitive plant is another. Sensitivity, speed, and delicacy of behavior are greatly enhanced in the more evolved animals when special organs for adaptive amplification have appeared.

Sense organs, or receptors — special cells or cell groups each particularly sensitive to one type of stimulus—enable the animal to become aware of and to respond to more and feebler environmental changes. Minute amounts of light excite the retina of the eye, only intense light affects the amoeba. And the eye discriminates light intensities, colors, and directions as the undifferentiated amoeba does not. Similar relations hold for the other sense receptors, for sound, touch, temperature, chemicals, etc. In like fashion, other cell groups, the effectors, have become specialized for response or action. The muscles produce movement which is more rapid, more powerful, more

graded, and more finely controlled than are the amoeba's movements. The glands make more specific and often more complex chemicals and release them at particular times and places. And other special effectors have been invented—electric shockers, light flashes, and the like.

Most important of these new organs for enhancing the behavioral capacities of animals is the nervous system. This serves to conduct, with great rapidity, the excitation set up at receptors and ultimately to deliver it to effectors; and it serves the more difficult function of sorting and directing and relaying these exciting messages so that the appropriate effectors are appropriately activated for each of the various stimuli which demands attention. The nervous system, then, serves as conductor, mainly via its long nerve strands and paths which connect to all parts of the body; and as coordinator or integrator, mainly via the nerve cells and fibers and their interconnections which constitute the mass of the central nervous system itself. (See Potentials, Bioelectric.)

Nearly all of the ten billion odd nerve cells, or neurones, of the body are gathered in the long spinal cord and its swollen upper end — the central nervous system which lies in the backbone and fills the cavity of the skull. Only a few neurones, gathered into small knots, or ganglia, are scattered among the other body tissues as parts of a subordinate, largely self-regulating (autonomic) nervous system, which helps control visceral activity—as the size of blood vessels, the movements of the digestive tube, secretion of saliva, the diameter of the pupil of the eye, the speed of the heart, and the like.

Each neurone has long extensions—branching dendrites which carry nerve impulses to the cell body and a mostly unbranched axon which carries away impulses, often for half the length of the body. These branches connect various neurones, an axon of one, (or more often of many) meeting, synapsing with, the dendrite of another (or many others). Receptors connect with the dendrites of sensory neurones, which run in the peripheral nerves; their axons connect with other neurones, nearby or in far portions of the central nervous system; soon or late, connections are made with motor neurones whose axons are again peripheral nerves and run to one or another muscle. This simple pathway—from receptor, through sensory, intermediate, and motor neurones, to effector—is the unit of neural function, the reflex arc.

Since impulses travel from neurone to neurone mostly along these anatomical tracks, the connections from each nerve are unique to it. The whole nervous system does not function as a single unit but as a coordinated group of units each with its particular duties. Thus simple reflexes—as pulling the foot or finger away from an injurious stimulus—are completed at whatever level of the spinal cord the relevant nerves connect. A dog with the lower cord cut from the remaining parts of the nervous system will still execute leg reflexes of pulling from an injury, scratching an irritation, even of stepping. But it will have no sensory experience of pain with the injury nor be able to move the legs voluntarily. The paths carrying sensory messages to regions of the upper brain, where they are interpreted, or motor messages from other regions of the brain, where

“voluntary” motion is initiated, have been interrupted.

Anatomical, physiological (such as the above), electrical, and other studies have elucidated in great detail the myriad interconnections within the nervous system and the special functions of each portion, as well as the general role of the whole. Thus, simple limb and body reflexes depend mostly on the spinal cord. Head reflexes and the control of many visceral actions (breathing, salivation, vomiting, regulation of blood pressure and heart rate, etc.) depend on the medulla oblongata, an oblong expansion of the upper cord. Above this, the midbrain is especially concerned with the control of posture and balance; injury here may make a man or animal unable to stand or walk smoothly. Still higher, the top of the older nervous system, is the thalamus, which largely controls the autonomic nervous system and is concerned with emotional expression, as of rage, fear, and pain.

The newer brain regions are the cerebellum, above the midbrain, and the cerebrum, above the thalamus. These have their neurone cell-bodies (which constitute the grey matter; the fibers make the white matter) on or near the surface, in an outer layer or cortex. And these cortexes have increased in relative and absolute size in the “higher” animals from mammals through man. The cerebellum coordinates voluntary movements and is larger as motor skills increase. The human cerebral cortex is as large as the remainder of the nervous system, and it is further especially subdivided into many regions with special functions—seeing, hearing, talking, etc. Yet somehow it continues to act as a single whole, for on its functioning



depends man's mind—his reasoning, remembering, and abstracting. It enables him to conceive a future and to direct his efforts towards one of his preference.

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University of Chicago.

#### NESSLER REAGENT FOR AMMONIA

Reagent—a solution of 10 gm. of mercuric iodide and 5 gm. potassium iodide in 50 cc. of water to which is added a solution of 20 gm. potassium hydroxide in 50 cc. water. A yellow to brown-red precipitate is obtained with ammonia or ammonium salt solutions.

Reference: Chem. Zentr. 1856, 529. Zeit. anal. Chem. 20, 225 (1881). Pharm. Zentralhalle 1900, 296; 1914, 972.

#### NET ENERGY

That part of the food energy which appears in the animal's products (milk, meat, eggs, wool, work). Metabolizable energy minus calorogenic effect of food.

M. K.

#### NEUBAUER'S THEORY OF TYROSINE METABOLISM

Tyrosine metabolism takes two paths; in one p-hydroxyphenyl pyruvic acid is formed, and in the other 2,5-dihydroxyphenyl alanine; both then form 2,5-dihydroxyphenyl pyruvic acid and then homogentisic acid; which then is decomposed to acetoacetic acid. Strongly ketogenic. (See Dakin's theory of tyrosine metabolism.)

#### NEUBERG ESTER

Hexosemonophosphoric acid; fructofuranose-6-monophosphate; present in muscle. See Carbohydrate Metabolism.

#### NEUBERG REACTION FOR PYRUVIC ACID, SUCCINIC ACID AND ALANINE, ARGININE, BETAINE, ETC.

A pine shaving moistened with hydrochloric acid turns red when heated with ammonium pyruvate, due to evolution of pyrrole. Ammonium succinate, heated with zinc dust, also gives the pyrrole reaction. The same reaction is given by the following on heating: Alanine, asparagine, betaine, cystine, diamonosuccinic acid, glycocoll, histidine, lipoic acid, leucine, sarcosine, taurine and tyrosine.

Reference: Zeit. physiol. Chem. 31, 574 (1901).

#### NEUBERG REAGENT FOR ALIPHATIC ALCOHOLS AND AMINO ACIDS

Alcohols and amino acids form crystalline compounds of high molecular weight with  $\alpha$ -naphthylisocyanate. The amino acids may be estimated quantitatively.

Reference: Ber. 1905, 2359. Biochem. Zeit. 1907, 456; 1909, 445.

#### NEUBERG TEST FOR GLYOXALIC ACID

A little naphthoresorcinol is added to 2 cc. of test solution and, after the addition of 5 cc. concentrated hydrochloric acid, the solution is heated to boiling. After cooling and diluting with water, the solution is shaken with ether; a violet or deep red color indicates glyoxalic acid.

Reference: Biochem. Zeit. 1910, 437.

#### NEUFELD PHENOMENON

The bactericidal and lytic effect of bile salts for certain streptococci, pneumococci, staphylococci, etc.

#### NEURAL ACTIVITY, MEMBRANE HYPOTHESIS OF

See Neurophysiology.

**NEURIDINE**

See Spermine.

**NEURINE**

Trimethylvinyl ammonium hydroxide; present in brain and other products; product of putrefaction of lecithin; forms a trihydrate and is a strong base.

**NEURINE TEST**

See Brieger.

**NEUROHUMORS**

Local nerve hormones, e.g. sympathetic.

**NEURONES**

See Nervous System.

**NEUROPHYSIOLOGY**

Neurophysiology is that branch of physiology concerned with the study of the biological functions of the nervous system. Although a tremendous amount of detailed and experimentally proven factual material has been brought to light (most of it in the last half-century) our exact knowledge regarding neural organization and functioning must be considered inadequate and relatively meagre. The following account will be concerned with some of the more general aspects of this branch of physiology.

The transmission of excitation or the conduction of nerve impulses forms the basis of all neural activity. Consequently, the nature of impulses in single nerve fibers has been the subject of much investigation. The membrane hypothesis, which is now generally accepted, supposes that depolarization of the fiber surface is, in fact, the nerve impulse. According to this theory, the polarized membrane breaks down locally under the action of the stimulus and so establishes a potential difference between the

active and inactive regions. Local currents thus set up, serve as the stimulus which makes neighboring segments active. The depolarization is instantaneous while restoration of the surface requires a certain time. During the first part of the period of restoration, the surface is unable to break down again, it is absolutely refractory, and thus the depolarization spreads down the fiber. Among the many aspects of neural activity which are of primary interest in this connection may be listed: the action potential of nerve; the refractory period; the all-or-none nature of conduction; antidromic conduction; velocity of conduction; metabolism of the nerve fiber; the respiration of nerve; chemical changes in nerve; the transmission of excitation at the neuromyal junction.

The simplest reaction of the nervous system is the spinal reflex, a reaction evoked by afferent impulses entering the spinal cord at the level from which the motor impulses emerge. Because of the enormous complexity of the central pathways, analysis demands that central conduction be studied in as simple a form as possible. For this reason, much attention has been devoted to the spinal reflex arcs. Each functional unit of the central nervous system is a cell which has no direct anatomical continuity with any other functionally related cell, action of one cell upon another being communicated solely through discontinuous interfaces. Foster and Sherrington introduced the term "synapse" (from the Greek, to clasp) to describe the relationship between contiguous neurons. In the reflex arc the passage of neural impulses is in one direction only, from the afferent or sensory neur-

ons to the efferent or motor neuron. This is because the synapse possesses a valve-like action which imposes a polarity on the direction of conduction. The reflex arc has been utilized in the study of the temporal and spatial summation of inadequate stimuli, the overlapping central distribution of afferent pathways resulting in the phenomena of convergence and occlusion, the principle of reciprocal innervation, reflex discharge and reflex tetanus, the nature of central excitation and inhibition, synaptic transmission and graded synaptic resistance.

The early phylogenetic development of the nervous system led to a central organ arranged in segments. In the lower worms each segmental ganglion exhibits a high degree of autonomy, so that most of its segmental activities are undisturbed by separating it from adjacent ganglia. The process of encephalization, which took place as the invertebrates developed and which occurred in an even more striking manner during vertebrate evolution, resulted in an ever increasing dependence of the aboral segments on the head ganglion or brain. With the increase in size and complexity of the brain there has been a tendency of this organ to take over, elaborate, and control functions which in lower forms are governed almost entirely by the individual segments. But even the spinal segments of man retain some small portion of the primitive autonomy and when the spinal cord of a carnivore is completely separated from the brain it remains capable of mediating simple items of behavior which are but slightly removed in character from similar movements evocable in the intact animal. When the lower parts of

the brain stem are left connected with the cord, more complex activity is possible. If only the cerebral cortex, the most recent and most complex product of encephalization, is removed in a cat or dog, the behavior deficit is even less. Study of these behavioral activities indicates that each level is organized to govern specific functions rather than to control anatomical units. In other words, the central nervous system is organized on the basis of what may be termed "levels of function."

Hughlings Jackson, in 1884, suggested that inhibitory impulses stemming from the higher or more rostral (and phylogenetically more recent) parts of the nervous system prevent the lower and more primitive levels from dominating behavior. Removal of the higher, more discriminative levels results in the release of certain more primitive and less integrated functions controlled by the more archaic portions of the cerebrospinal axis. In working with decerebrate animals, Sherrington found that this concept of Jackson's was eminently sound. In the case of the decerebrate preparation the most striking release phenomenon is the greatly exaggerated tone which is present in the extensor muscles due to the release of a vestibulo-spinal mechanism from higher extrapyramidal control. Because reflex responses can be predicted and easily evoked in the unanesthetized decerebrate animal, this preparation in the acute state enabled Sherrington to formulate many basic concepts of reflex action and integration. Recently Macht and Bard have prepared decerebrate cats which they were able to maintain and study for periods ranging up to five months after operation.

Surgical ablation is one of the most extensively used experimental methods in neurophysiology. Analysis of the capacities and abnormalities of different animals in the spinal, decerebrate and decorticate states has been responsible for much of our knowledge concerning the integration and working of different functional levels.

Postural coordination and its central control have received much attention since Sherrington's early work on decerebrate rigidity, Liddell and Sherrington's investigations of the stretch or myotatic reflex, and the studies of Magnus and De Kleyn on attitudinal and righting reactions. All phases of the postural mechanism are influenced by the cerebral cortex although many basic reactions are integrated in the medulla oblongata. The righting reactions are for the most part dependent upon the integrity of the midbrain, although recent experimental work indicates that some of these reflexes are elaborated by cats from which all neural tissue rostral to the pons has been extirpated. Tonic labyrinthine reflexes include the acceleratory reflexes and the positional reflexes. The former arise in the semicircular canals and are responsible for a group of special reactions involving the eye (vestibular nystagmus) and the skeletal muscles. The positional reflexes arise from the otolithic maculae of the labyrinth, and have to do principally with the righting reactions.

Studies of sensation or the mechanism involved in the transmission of afferent impulses from specific receptors of the body to certain way stations in the brain where these impulses are translated into the "awareness" of sensory experi-

ence, constitute an important field of neurophysiology. The great sensory ganglion of the brain stem is the dorsal thalamus; all somatic sensory impulses must pass through this portion of the diencephalon before being forwarded to the cerebral cortex. Extensive clinical and experimental investigations of the role played by the thalamus in sensation have been carried out by Head and Holmes, Dusser De Barenne and others. Impulses from the dorsal thalamus pass to the somatic sensory area of the cortex. The outstanding feature of cortical sensibility is the recognition of fine detail in sensation. Various methods have been employed in attempts to determine the position and extent of the somesthetic area of the cortex. The effects of cortical lesions, electrical stimulation of the intact brain in unanesthetized patients, and additional clinical studies by Cushing, Foerster and others indicate the existence of a well-defined segmental localization of sensory function in the parietal lobes. A far more detailed picture of cortical sensory representation has been obtained as a result of the discovery by Marshall, Woolsey and Bard that the application of a discrete tactile stimulus to a cutaneous area produces in the cortex of the anesthetized animal a well-localized potential wave. These authors have been able to demonstrate very accurately the representation of tactile sensibility in the monkey's cortex as revealed by the cortical potentials set up on stimulation of touch receptors in different parts of the contralateral half of the body.

The autonomic nervous system is the efferent pathway to the visceral effectors. The distinction between the autonomic and the cerebrospinal

systems is a functional rather than an anatomical one. Anatomically, the two are continuous rather than distinct; the autonomic being a visceral extension of the cerebrospinal. Functionally, they are different in that the cerebrospinal controls skeletal muscle, while the autonomic innervates visceral effectors (glands, smooth muscle, and cardiac muscle). Skeletal muscle fibers are connected with the central nervous system by motor neurons which have their cell bodies in the brain or spinal cord, and there is only one nerve cell between the cerebrospinal axis and the effector. The innervation of the viscera, on the other hand, is characterized by the fact that the path from the central axis to the effector is broken by a synapse and the axon directly in contact with the effector is part of a neuron which lies entirely outside the central nervous system. The cranial and sacral outflows of the autonomic comprise the parasympathetic system, while the thoraco-lumbar division is usually called the sympathetic system. Most of the visceral tissues possess a double nerve supply, parasympathetic and sympathetic. Wherever this occurs, the two systems, as a rule, exert opposed or antagonistic effects.

Cannon and his coworkers have emphasized the fact that the sympathetic system tends to go into action as a whole in situations which require an emergency response. The action of the sympathetic leads to an increase of the available potential energy by increasing the amount of sugar in the blood. Unnecessary activity of the digestive system is stopped. Acceleration of the heart and peripheral vasoconstriction produces a more rapid circulation through active tissue. Respiratory processes

are aided by dilation of the bronchioles. In other words, there is an integrated body of activity directed toward the mobilization of energy, protection of the organism, and maintenance of the milieu intérieur in the face of an emergency situation. Conditions under which the sympathetic acts include pain, asphyxia, emotional excitement, exposure to cold, hypoglycemia, and vigorous muscular exercise. Neural stimulation of the adrenal medulla causes the secretion of a chemical agent, adrenin, capable of inducing practically all of the changes which occur when the entire thoraco-lumbar outflow is active. Cannon and others have demonstrated that a sympathico-mimetic substance is given off into the blood stream when impulses in postganglionic sympathetic fibers induce a change in effector cells. This substance, to which has been given the name, sympathin, has properties similar to adrenin and acts in conjunction with it.

The parasympathetic division of the autonomic system does not go into action as a whole. Its restricted distribution enables it to exert effects upon single organs without affecting the other viscera. Likewise, there is an absence of any parasympathetic hormone analogous to the adrenin of the sympathetic system which is capable of acting extensively upon organs innervated by this system. While there is good evidence that a chemical agent, acetylcholine, is the transmitter of excitation and inhibition at parasympathetic postganglionic endings, this substance is not capable of exerting widespread effects because of its very rapid hydrolysis through the agency of cholinesterase.



In this brief account, no mention has been made of the functions of the cerebellum, basal ganglia, special senses, the motor areas of the cerebral cortex, the pyramidal and extrapyramidal motor system, the hypothalamus or the electroencephalogram. For a detailed account of these and other subjects within the province of neurophysiology, the reader is referred to the sources listed below.

The most challenging problem presented by the nervous system is the explanation and elucidation of mental phenomena. However, it must be admitted that the neurophysiologist has made little progress in this direction. Analysis of mental experience in terms of reflex action and neural organization is still completely unsatisfactory. The principal advances in this connection have been made by the physiological psychologist through the use of conditioned reflex experiments and other special methods.

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#### BIBLIOGRAPHY

- Bard, P.: *Macleod's Physiology in Modern Medicine*, St. Louis, 1941, Mosby.  
Fulton, J. F.: *Physiology of the Nervous System*, New York, 1938, Oxford University Press.  
Sherrington, C. S.: *Integrative Action of the Nervous System*, New Haven, 1906, Yale University Press.  
Magnus, R.: *Körperstellung*, Berlin, 1924, Julius Springer.  
Adrian, E. D.: *The Basis of Sensation*, New York, 1928, W. W. Norton and Co.  
Cannon, W. B.: *Bodily Changes in Pain, Hunger, Fear, and Rage*, New York, 1929, D. Appleton-Century Co.  
Cannon, W. B.: *The Wisdom of the Body*, New York, 1939, W. W. Norton and Co.

Pavlov, I. P.: *Conditioned Reflexes*, Oxford, 1927, Oxford Univ. Press.

Herrick, C. J.: *Neurological Foundation of Animal Behavior*, New York, 1924.

Kuntz, A.: *The Autonomic Nervous System*, Philadelphia, 1934, Lea and Febiger.

See also NERVOUS SYSTEM.

#### NEUROSYPHILIS

See Fever Therapy.

#### NEUTRON RAYS, BIOLOGICAL EFFECTS OF

The neutron of mass 1 but possessing no charge, can be ejected with varying amounts of energy in cyclotron disintegrations of matter. It has biological effects comparable but also different from those produced by X-rays. It operates chiefly by the production of ionization in tissue. In the last decade techniques of generation and the measurement of the quantity of radiation have been developed so that one might estimate tissue doses. Retardation of growth of normal and malignant tissues have been noted. Bacteria have been killed and bacteriophage has been inactivated. In every case a quantitative difference exists, principally in favor of dosing with neutrons. Therapeutic results in cancer cases are encouraging when fast neutrons are used. Slow neutrons exercise an enhanced effect in the presence of boron compounds which have been introduced into neoplastic tissue.

Reference: P. C. Aebersold and J. H. Lawrence, *Annual Reviews of Physiology* IV, 25-48 (1942).

See also Radiation, Biological Effects of, Water Metabolism.

#### NICOL PRISM

A specially constructed piece of calcite or Iceland spar ( $\text{CaCO}_3$ ), which when ordinary light is passed through, causes the emitted light to vibrate in only



one plane; i.e. to be plane polarized.

# **NICOTELLINE**

$C_{10}H_8N_2$ ; an alkaloid of tobacco. Aqueous solution is neutral. Colorless needles m.p. 147-148°.

# **NICOTIMINE**

$C_{10}H_{14}N_2$ ; an alkaloid found with nicotine. Colorless alkaline oil, b.p. 250-255°. Aurichloride forms yellow leaflets, m.p. 182-185°.

# **NICOTINAMIDE TEST**

See Vilter-Spies-Mathews.

# **NICOTINE**

$C_{10}H_{10}N_2$ ; 1-methyl-2-(3'-pyridyl)-pyrrolidine, or pyridyl-N-methylpyrrolidine; chief alkaloid of tobacco; colorless oil, b.p. 246.1° 730.5 mm. Causes transient stimulation, then paralysis of autonomic ganglia. Largest use is as an insecticide. Fatal dose: 1-4 drops, effect usually rapid; chemical antidotes, tannic acid, hydrogen peroxide, intracardiac injection of epinephrine.

# **NICOTINE TEST**

See Reichard.

# **NICOTINIC ACID**

$C_6H_5O_2N$ , m-pyridine carboxylic acid; precursor of pellagra preventing factor of B complex and cures dog disease, "black tongue."

# **NICOTINIC ACID AMIDE**

See Pellagra Preventive Factor.

# **NICOTINIC ACID, ROLE IN PLANTS**

See Plant Growth Hormones.

# **NICOTINIC ACID TESTS**

See Swaminathan, Vilter-Spies-Mathews.

# **NICOTOINE**

An alkaloid,  $C_8H_{11}N$ , from Turkish tobacco; b.p., 208°.

# **NICOTYRINE**

$C_{10}H_{10}N_2$ ; alkaloid of tobacco. Oil b.p. 280-281°. On dehydration yields nicotine, which it resembles physiologically.

# **NIDATION**

The first stage (8 to 10 days) of the establishment of a fertilized ovum in the walls of the uterus.

# **NIGHT BLINDNESS**

See Eye, Biochemistry of

# **NINHYDRIN REACTION**

Alpha amino acids or compounds containing the  $\alpha$ -amino group give a color ranging from deep blue to violet or even to red when treated with ninhydrin solution. In a 1:10000 solution, glycocoll and alanine give a blue color; tyrosine gives the color at 1:5000. Reference: J. Chem. Soc. 97, 2025 (1910). J. Biol. Chem. 20, 217 (1915).

# **NIRVANOL**

5, 5 - phenylethyl - hydantoin, m.p. 199°, a hypnotic and sedative.

# **NISINIC ACID**

A 24 carbon unsaturated fatty acid with 6 double bonds, found in cod liver, herring, shark liver oils.

# **NITELLA**

See Permeability, Protoplasm.

# **NITRATASE (BACT. COLI) NITRATE REDUCTASE**

An enzyme of the extracts of Bact. coli which catalyzes the reduction of nitrate to nitrite; not well known.

# **NITROGEN BALANCE**

The ratio of nitrogen (protein) intake and output. Positive N balance indicates retention of protein, and tissue building; negative

N balance indicates loss of protein, and tissue destruction.

# **NITROGEN EQUILIBRIUM**

The condition of having equal nitrogen (protein) intake and output. Indicates equilibrium of tissue building and destruction. See Nitrogen Balance.

# **NITROPRUSSIDE REACTION**

See Cyanide-Nitroprusside Reaction.

# **NITROSOMONAS**

See Microbiology.

# **NONOSE**

Any monosaccharide with the formula  $C_9H_{18}O_9$ . There are none naturally occurring.

# **NON-PROTEIN NITROGENOUS CONSTITUENTS**

See Amino Acids, Physiology of.

# **NON-PROTEOLYTIC ENZYMES**

See Enzymes, Non-Proteolytic.

# **$\pi$ -NORCAMPHOR**

See Santenone.

# **d-NORLEUCINE**

$C_6H_{13}O_2N$ ;  $\alpha$ -amino - n - caproic acid, m.p.  $285^\circ$ ; an amino acid found in nerve tissue protein, and rarely in other proteins.

# **NORMAL**

(1) A measure of concentration of a solution, equal to one gram equivalent of solute per liter of solution.

(2) In organic chemistry the designation applied to straight carbon chain aliphatic compounds.

# **NORNICOTINE**

$C_8H_{12}N_2$ ; 2 - (3 - pyridyl) - pyrrolidine; an alkaloid of tobacco. Properties vary depending on origin; b.p. about  $139-140^\circ/12$  mm. Physiologically similar to nicotine.

# **NOVOCAINE**

See Procaine.

# **NOVOCAINE TEST**

See Young.

# **NUCLEASES**

Enzymes which hydrolyze nucleic acids.

# **NUCLEIC ACIDS**

The prosthetic group of the nucleoproteins. Four nucleotides (which see) combine to make up one molecule of nucleic acid. On hydrolysis all nucleic acids yield 2 purine bases, usually guanine or adenine, 2 pyrimidine bases, usually cytosine, thymine, uracil, or 5-methyl cytosine; phosphoric acid, and a carbohydrate, ribose or desoxyribose. The nucleic acids are vital to the life process. A decrease in the amount of nucleic acid in the body is associated with old age. Chromosomes are nucleic acids plus protamin, the combination existing as chromatin. On dissolving the protein from chromosomes the nucleic acid remains in bands that appear to be associated with the genes.

The exact chemical structure is in doubt, but probably the pyrimidines are connected to the carbohydrates through a glycosidal linkage at  $N_8$ , and the purines similarly through  $N_7$ . The sugars have the  $\delta$ -oxide structure.

In general the nucleic acids may be classed as (1) pyrimidines or amino, and oxy derivatives of pyrimidines, e.g. cytosine, alloxan; (2) purines or amino and oxy derivatives of purine, e.g. adenine, xanthine, caffeine, pterins; (3) nucleosides or purine or pyrimidine N-glycosides, e.g. adenosine, uridine, vicine; (4) nucleotides or phosphoric acid esters of nucleosides, e.g. adenylic acids, cozy-

mase, partly depolymerized nucleic acids and nucleic acids in increasing order of molecular complexity.

**NUCLEIC ACID TEST**

See Steudel.

**NUCLEIN**

A combination of protein and nucleic acid, the protein being in most cases of somewhat smaller molecular weight than the protein in nucleoprotein, from which nuclein may be derived by partial hydrolysis.

**NUCLEOPROTEINS**

In the American classification of proteins, the nucleoproteins consist of one or more protein molecules with nucleic acid.

Example: nuclein.

**NUCLEOSIDASE.**

See Enzymes, Non-Proteolytic.

**NUCLEOSIDES**

A purine or a pyrimidine with a molecule of a carbohydrate; may be derived from a nucleotide by

the loss of phosphoric acid. See Guanosine, Adenosine.

**NUCLEUS**

See Protoplasm.

**NUCLEOTIDES**

See Mononucleotides.

**NUCLEOTIDASE**

See Enzymes, Non-Proteolytic.

**NUTRIACHOLIC ACID**

$C_{24}H_{40}O_5$ , m.p.  $198^{\circ}$ ; a bile acid found in the beaver.

**NUTRITION**

See Amino Acids, Physiology of.

**NUX VOMICA**

Dried ripe seeds of *Strychnos nux vomica* containing alkaloids strychnine and brucine; a heart tonic and is also used in dyspepsia.

**NYCTALOPIA**

Night blindness; see Vitamin A.

**NYLANDER-ALMEN TEST**

A test for reducing compounds, whereby alkaline bismuth subnitrate is reduced to metallic bismuth.

## OBSTETRIC DRUGS

See Ergot.

## n-OCTACOSANOL

$C_{28}H_{58}O$ , a constituent of apple cuticle.

## OCTOSE

Any monosaccharide with the formula  $C_8H_{16}O_8$ . There are none naturally occurring.

## ODONTOBLASTS

See Teeth, Biochemistry of.

## OEDEMA

See Edema.

## OENIN

A glycoside of the skin of purple grapes, consisting of glucose and oeninidin.

## OESTRADIOL

See Estradiol.

## OESTRIN

See Estrin.

## OESTRIOL

See Estriol.

## OESTRONE

See Estrone.

## OFFER TEST FOR URIC ACID

Uric acid reduces an alkaline solution of phosphomolybdic acid, even in the cold, forming a blue color. A deep blue precipitate of hexagonal prisms is obtained if 0.05% or more uric acid is present.

Reference: Zent. Physiol. 8, 801 (1906). Chem.-Ztg. 1898, 330. Wiener med. Blätter 1901, 405; 1902, 405. Biochem. Zeit. 161, 130 (1925).

## OKUDA-NISHIJIMA REACTION FOR CYSTEINE

A small quantity of cysteine solution is treated with a few drops of faintly acid zinc chloride solution and a freshly prepared aqueous sodium nitroprusside solution. Ammonia or sodium hydroxide is added until zinc hydroxide precipitates; a ruby-red color, stable for several hours, is formed.

Reference: Bul. Sci. Fakultato Terkultura Kjusu Imp. Univ. 2, 209 (1928).

## OLEANDRIN

Glycoside composed of digitalose and digitaligenin.  
See Digitalis.

## OLEIC ACID

An unsaturated liquid fatty acid,  $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$ ; found in most fats and oils; m.p.  $14^\circ C$ .

## OLEORESINS

The sticky exudate of pine or fir trees, consisting of a solution of resin acids in essential oils. On standing the essential oils evaporate, leaving a hard glass-like resin.

**OLIGOMENORRHEA**

Abnormal prolongation of time intervals between menstruations. Etiology same as for Amenorrhea (which see).

**ONCOTIC PRESSURE**

The osmotic pressure of colloids, e.g. blood plasma has a pressure of 28 mm. Hg.

**OO-**

Prefix signifying "egg" or "ovum."

**OÖGENESIS**

The origin of the female germ cell or egg.

**OPHTHALMIA**

See Conjunctivitis.

**OPHTHALMOLOGY, CHEMICAL**

See Eye, Biochemistry of.

**OPIAN**

See Narcotine.

**OPIANIN**

See Narcotine.

**OPIN**

See Porphyrroxine.

**OPIUM**

The dried latex of unripe capsules of *Papaver somniferum*, contains numerous alkaloids, as morphine, codeine, narcotine; used as a narcotic, in cough medicines and to control diarrhea; laudanum is a tincture of 1% morphine content; paregoric is a twentieth the strength of laudanum.

**OPSONIN**

See Immunological Phenomena.

**OPTICAL ACTIVITY**

The ability possessed by certain chemicals to rotate the plane of polarized light when the latter is passed through the substance. See Specific Rotation.

**OPTICAL ROTATION**

The number of degrees of rotation that an optically active substance produces in the plane of polarized light for a given length of passage.

**OPTOCHIN**

Ethylhydrocupreine, made by hydrogenating quinine, then demethylating and ethylating; pneumococcicidal even in dilutions of 1 to 400000 in serum.

**ORCIN**

See Orcinol.

**ORCINOL**

Orcin, 3,5-dihydroxytoluene, 5-methyl-resorcinol; m.p., 58° (107° when anhydr.); b.p. 290°; occurs in many species of lichens and is used as reagent in test for sugars.

**ORCINOL-HYDROCHLORIC ACID TEST**

A test for pentoses depending on the formation of blue green or violet colors when a sugar is heated with HCl and orcinol.

**ORGANIC GROWTH**

See Growth.

**ORGANIZER (SPEMANN'S)**

A chemical substance, probably of the sterol type, in the gastrula, which can organize primitive cells to develop according to the development pattern of its source.

**ORLOW REACTION FOR LECITHIN**

A mixture of alcoholic solutions of lecithin and alloxan gives a pink to red color and a red precipitate is produced.

Reference: Farm. Zhur. 1903, 1657.

**ORNITHINE**

$\text{NH}_2\text{CH}_2(\text{CH}_2)_2\text{CHNH}_2\text{COOH}$ ; a basic amino acid; diamino valeric acid; obtained from arginine by splitting off urea; found in

the urine and excrement of fowls. On decomposition it gives rise to putrescine.

See Detoxication.

See also Arginase.

## ORNITHINE CYCLE

The formation of urea in a cycle involving the addition of 2 molecules of ammonia and 1 of carbon dioxide and the abstraction of water from ornithine to produce citrulline, the addition of ammonia and the abstraction of water to citrulline to produce arginine, and the decomposition of arginine by arginase to form urea and to reform ornithine for another cycle; this amounts to the synthesis of urea from ammonia and carbon dioxide; the site of action is the liver.

## ORNITHINE TEST

See Herzog.

## ORNITHURIC ACID

Ornithine dibenzoate; the detoxification product of benzoic acid by birds (analogous to the formation of hippuric acid by mammals).

## OROBOSIN

See Flavonol Glycosides.

## OROSIN

A term suggested for associated coagulable serum protein systems.

## OROTIC ACID

4-uracilcarboxylic acid, a pyrimidine found free in milk.

## ORTHOCELLULOSE

A little used name for pure cellulose.

## ORTHOSTATIC PROTEINURIA

The appearance of protein in the urine of certain few individuals when they stand erect.

## ORYZANIN

A name originally applied to the

crude thiamine chloride preparations, now sometimes used for the pure substance.

## ORYZENIN

A glutelin from rice.

## OSAZONE

The reaction product of two molecules of phenylhydrazine with one molecule of sugar. The two molecules of phenylhydrazine add on to the carbonyl carbon and the one adjacent to it. Useful in the identification of the sugars.

## OSMOL OR OSM

The amount of electrolyte equivalent in osmotic pressure to that of a molar or molal solution of non-ionized solute.

## OSMOSIS

See Protoplasm.

## OSMOTIC PRESSURE

The pressure observed between solutions of different concentrations separated by a membrane permeable to the solvent but not the solute, due to the greater diffusion of solvent molecules from the dilute to the concentrated solution. The osmotic pressure of one mole of solute per liter is 22.4 atmospheres.

See Protoplasm.

## OSONE

A 1,2-dicarbonyl derivative of sugars. Obtained by heating an osazone with fuming HCl, thus splitting off the two phenylhydrazine groups.

## OSSEIN

An albuminoid of the matrix of bone, apparently identical with collagen.

## OSSEOMUCOID

A mucoid of the matrix of bone.



**OSTEOARTHRITIS**

See Arthritis.

**OSTEOBLASTS**

Embryonically active cells which form bone.

**OSTEOCLASTS**

Bone-destroying cells which make way for rearrangement and growth.

**OSTEOMALACIA**

See Rickets.

**OSTEOMYELITIS**

See Fever Therapy.

**OSTEASTEROL**

A sterol,  $C_{29}H_{48}O$ , isomeric with stigmasterol and possessing two double bonds; present in oysters and clams and probably replaces cholesterol in all the Lamelli-branchiata.

**OSYRITIN**

See Rutin.

**OUABAIN**

Acocantherin;  $C_{29}H_{44}O_{12}$ ; m.p.  $187^{\circ}$ ; Gratus (G) Strophanthin; glycoside from Strophanthus gratus, composed of rhamnose and ouabagenin; used as cardiac stimulant.

See Digitalis.

**OVALBUMIN**

Egg albumin; m.w. about 40,000; obtained from egg white.

**OVARY**

Germanium; german; female sex gland where hormones and ova are produced.

**OVOFLAVIN**

Riboflavin.

**OVOVITELLIN**

See Vitellin.

**OXALIC ACID**

m.p.  $189.5^{\circ}$  anh., occurs in many

plant cells free and as K acid salt or Ca salt in lichens and moulds.

**OXALIC ACID TEST**

See Schmalfuss-Werner-Kraul, Wagenaar.

**OXALURIC ACID**

The form in which part of oxalic acid is excreted in the urine.

**OXIDASE**

See under specific name, as "amine oxidase," etc.

**OXIDASES**

Respiratory enzymes which catalyze oxidation by oxygen.

**OXIDATION**

(1) The loss of one or more electrons by a substance being oxidized. (2) The exothermic combination of a compound with oxygen, or the loss of hydrogen from the compound. This is the source of energy of living matter.

**$\alpha$ -OXIDATION MECHANISM**

See Carbohydrate and Fat Catabolism.

**$\beta$ -OXIDATION OF**

**FATTY ACIDS THEORY**

Knoop's theory, advanced in 1904, that fatty acids are metabolized by losing 2 carbons at a time, due to oxidation at the  $\beta$ -carbon, preceded by desaturation of the molecule. See Carbohydrate and Fat Metabolism.

**OXIDATION-REDUCTION**

**POTENTIAL**

The e.m.f. developable by a system capable of mutual oxidation and reduction. It is due to the flow of electrons from the oxidant to the reductant. Usually the potential is referred to an external standard electrode, as a standard hydrogen or calomel electrode. Example: ferrous sulfate—ferric sulfate.

**OXIDATIVE QUOTIENT**

See Meyerhof Quotient.

**OXIDIGITONIC ACID**

See Digitalis.

**OXINE REAGENT**

See Hahn.

**OXIREDUCTASES**

Dehydrogenases.

**OXOCYCLO-DESMOTROPY**

Tollen's formulation of sugar structure showing an oxygen ring to explain the masking of the ketonic oxygen.

**OXONIUM**

See Hydronium.

**OXYACANTHINE**

An alkaloid,  $C_{37}H_{40}N_2O_6$ ; m.p., 216-217°; from root of berberis vulgaris; causes stomach pains and salivation; affects respiration and is said to cause mydriasis.

**OXYCELLULOSE**

The product of progressive action of oxidizing agents on a cellulose, like cotton.

**OXYCHOLESTEROL TESTS**

See Golodetz, Rosenheim.

**OXYGENASE (BACH)**

A system capable of converting oxygen into a peroxide (Bach).

**OXYGEN DEBT**

The partial asphyxia due to violent exercise or the like.

**OXYGEN POISONING**

A body fall in temperature of rats produced by exposure to oxygen at 4 atmospheres pressure.

**OXYHEMOGLOBIN**

The loose combination of hemoglobin with oxygen, which takes place in the lungs. The compound loses the oxygen to the tissues becoming reduced hemoglobin.

The iron is in the ferrous state.

See Hemoglobin.

**OXYHEMOGLOBIN TESTS**

See Michel Reagent, Rivat.

**OXYNITRILASE**

See Enzymes, Non-Proteolytic.

**OXYPROLINE**

See L-Hydroxyproline.

**OXYPROTEIC ACIDS**

A term sometimes used for sulfur-containing peptides.

**OXYREDUCASE**

A component of the fermentation group of enzymes, that, in conjunction with cozymase causes a Cannizzaro reaction to take place with aldehydes.

**OXYRENIN**

(Raymond Jonnard, 1942)

Some recent studies have shown that one of the causative factors in the genesis of "renal hypertension" might be a deviation of the metabolism of the aminophenols and phenolic amino acids. Schroeder,<sup>1</sup> and Schroeder and Adams<sup>2</sup> furnished experimental and clinical evidence showing that the alpha phenolase, "tyrosinase," inactivates the pressor amines, tyrosine, tyramine, adrenaline, and also to some extent renin under definite conditions, and is capable of reducing the blood pressure when injected in patients with "essential hypertension" due to hydronephrosis or to renal ischemia of the Goldblatt type. However the experiments of Bing<sup>3</sup> and of Holtz and co-workers<sup>4</sup> would rather suggest that the enzymatic destruction of the kidney pressor factor proceeds in the organism by way of a deamination reaction. In fact, angiotonin and renin are inactivated by the deaminase used in the experiments of the Croxattos.<sup>5,7</sup> This enzyme differs

from tyrosinase in a number of biochemical properties which preclude the possibility of the two possible reactions proceeding together on the same molecule. That both types of inactivation mechanism may play a role in the organism is suggested by the experiments of Holtz showing that in the presence of kidney tissue the phenolic amino acids (l-dopa, tyrosine, etc.) are decarboxylated under anaerobic conditions (as in kidney ischemia probably) to the state of hydroxytyramine or like hypertensor bodies, while their deamination to the state of dihydroxyphenyl acetic acid or like bodies is an aerobic reaction. Although Mason, Evers and Blacklock<sup>2</sup> found the oxygen consumption identical in the normal and in the ischemic kidney, Werle, Madlener and Herman<sup>3</sup> found the deamination process increased and the decarboxylation process reduced after ischemia of the kidney in situ. Contrary to this, however, the injection of l-dopa into an ischemic kidney in situ is followed by a strong hypertensive reaction similar to that produced by the presence of hydroxytyramine in the organism (Bing).<sup>3</sup>

A possible relationship of the above deamination-decarboxylation reactions to the presence of blood pressure active substances in the mammalian kidney is suggested by the experiments of Hermann and Bacq<sup>10</sup> showing that the enzymatic destruction oxidation (by a vegetable phenolase) of pressor bodies like adrenaline and tyramine proceeds, under suitable conditions, through the intermediate state of a strongly hypotensive substance (adrenoxine).

That a similar behavior is exhibited also by renin has been

recently demonstrated by Jonnard.<sup>11</sup> The progressive oxidation of pure "renin E" by a vegetable phenolase has been carried out to the state of a heretofore unidentified hypotensive substance which has a prolonged effect upon the arterial blood pressure of dogs and cats. The reaction is somewhat accelerated by the presence of diphenols, and particularly resorcinol (whose oxidation products are known to be without harmful effect upon the mammalian organism).

Awaiting further information concerning the chemical nature of the new hypotensive substance resulting from the oxidation of renin E, it is suggested to name it "OXY-RENIN."

The experiments illustrated here bear a remarkable similarity to those of Hermann and Bacq, only the time scale being considerably lengthened. They are also interesting in regard to the observation of Martin, Ichniowsky, Wisansky and Ansbacher<sup>12</sup> who have shown that the enzymatic inactivation of some pressor amines can be enhanced by a number of phenolic substances among which is l-dopa, whose anaerobic decarboxylation in the ischemic kidney yields a strongly pressor substance, probably hydroxytyramine.

#### BIBLIOGRAPHY

- <sup>1</sup> H. A. Schroeder: Science, 93: 116, 1941.
- <sup>2</sup> H. A. Schroeder and M. A. Adams: J. exp. Med., 73: 531, 1941.
- <sup>3</sup> R. J. Bing and M. B. Zucker: J. exp. Med., 74: 235, 1941.
- <sup>4</sup> P. Holtz, K. Credner and H. Walker: Zeits. f. physiol. chem., 262: 111, 1939.
- <sup>5</sup> H. and Croxatto: Science, 95: 101, 1942.
- <sup>6</sup> H. and R. Croxatto: Rev. Soc. argent. de Biol., 22: 439, 1941.

<sup>7</sup> H. and R. Croxatto: Proc. Soc. Exp. Biol. and Med., 48: 392, 1941.

<sup>8</sup> M. F. Mason, R. Evers and A. Blacklock: Proc. soc. exp. biol. and Med., 36: 819, 1937.

<sup>9</sup> E. Werle, M. J. Madlener and H. Hermann: Zeits. f. exp. med., 107: 252, 1940.

<sup>10</sup> P. Herman and Z. M. Bacq: Arch. int. de physiol., 50: 100, 1940.

<sup>11</sup> R. Jonnard: Am. Chem. Soc., 104th Meeting, Sept. 1942.

<sup>12</sup> G. J. Martin, W. A. Wisansky and S. Ansbacher: J. A. Chem. Soc., 63: 1771, 1941.

## OXYTOCIC DRUGS

See Pharmacology.

## OXYTOCIN

A polypeptide hormone of the posterior lobe of the pituitary. Causes contraction of smooth muscle fibres.

## OZONIDE

The product formed by the addition of ozone ( $O_3$ ) to a double bond. It has the structure which on hydrolysis breaks between the two carbons, thus affording a means of determining where the original double bond was.

## P

### PACE-MAKER

The substance whose rate of reaction in a series of linked reactions sets the pace for the series; lactic acid may be considered as the pace-maker in fermentation.

### PACINI-TARAS TEST FOR VITAMIN A IN OILS

One drop of oil, treated with 1 drop of guaiacol, 2 drops phenol and 1 cc. perchloric acid in 5 cc. chloroform, forms a purple color, developing into bright red. The color appears specific for vitamin A.

Reference: J. Am. Pharm. Assoc. 26, 721 (1937).

### PADUTIN

See Kallikrein.

### PAEONIN

Peonin; anthocyan from deep violet-red peonies, the diglucoside of cyanidinmonomethylether.

### PAGET REACTION FOR ADRENALINE AND ADRENALONE

An adrenaline solution gives a reddish-brown or amber color with 10% ammonium molybdate solution, which changes to a greenish fluorescence after the addition of sodium hydroxide. Adrenalone forms a yellow color or yellow-orange precipitate which is not changed with sodium hydroxide.

Reference: Bull. sci. pharmacol. 37, 537 (1930).

### PAIN

See Wound Healing.

### PALEONTOLOGY

The study of fossil organisms.

### PALEOZOIC ERA

Era of invertebrates; includes the permian, carboniferous (amphibians), devonian (fishes), silurian (invertebrates), cambrian.

### PALMITIC ACID

A saturated fatty acid,  $\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$ ; found in animal and vegetable fats; m.p. 63-4° C.

### PALMITOLEIC ACID

A 16 carbon single double bond unsaturated fatty acid of cod liver and herring oils.

### PALUDISM

See Malaria.

### PANCREAS

See Gastro-Enterology.

### PANCREATIC ACTIVITY TEST

See Winternitz.

### PANCREATIC ENZYMES

These include pancreatic amylase (amylase), maltases, lactases, sucrases; lipase (steapsin); proteolytic enzymes, as trypsin, chymotrypsin, heterotrypsin, poly-

peptidases, dipeptidases; enterokinase activator.

### PANCREATIC JUICE

The external secretion of the pancreas; aids digestion; has a pH of 7.5-8.0; is 98.7% water, the remainder being various enzymes, organic and inorganic compounds.

### PANCREATIC PROLIPASE

An inactive thermolabile protein of pancreatic extracts, which in the presence of tissue extracts becomes an active fat hydrolyzing enzyme.

### PANCREATITIS

See Gastro-Enterology.

### PANCREATROPIC PRINCIPLE

The hormone of the anterior pituitary which controls the islets of Langerhans and their insulin production and action.

### PAN-ENDOSCOPE

See Urology.

### PANSECRETIN

See Secretin.

### PANTOTHENIC ACID

Probably the most important constituent of "bios" or "yeast growth substance," now known to have the constitution  $\alpha$ -gamma - dihydroxy - beta - beta - methyl-butyr alanine or  $\text{CHOHC}(\text{CH}_3)_2\text{CHOHCONHCH}_2\text{CH}_2\text{COOH}$ , and to have vitamin properties. It is freed from a bound condition by enzyme action. Its deficiency is shown by gray hair, adrenal necrosis, kidney complications, ulcers in the intestinal tract in hogs, dogs, mice, rats and chicks. Feeding extra pantothenic acid increases hatchability of eggs. Pantothenic acid is low in the blood of patients with riboflavin deficiency, beriberi and pellagra.

### PAPAIN

Papayotin; vegetable pepsin; an intra-cellular proteinase of the pan-pan tree, *Carica Papaya*; activated by glutathione and other SH containing compounds, by HCN, and by photokinase; shows an optimum pH between 4 and 7.

### PAPAINASES

A group of intracellular proteinases in plants with an optimum pH of 4-7. Papain is a typical example. They are inactivated by copper salts and iodoacetate and activated by SH compounds and cyanide.

### PAPAVERINE

$\text{C}_{20}\text{H}_{21}\text{O}_4\text{N}$ ; prisms or needles, m.p.  $147^\circ$ ; opium alkaloid of the benzyl isoquinoline group; weakly poisonous, large doses causing mild tetany; used as antispasmodic since it paralyzes smooth muscle.

### PAPAYOTIN

See Papain.

### PAPILLA

See Hair.

### PARABIOSIS

The joining together of two living individuals; particularly, the artificial junction in order to study the effect of one on the other.

### PARACASEIN

The product of the action of the enzyme rennin on casein.

### PARAHEMATINS

Haematin combined with certain denatured proteins and bases, the combination being with 2 molecules of base, and the iron being in the ferric state.

### PARAMORPHINE

See Thebaine.



**PARANUCLEIN**

1. The essential substance of true nucleoli.
2. A nuclein derived from cytoplasm.

**PARASYMPATHETIC,  
DRUGS FOR DEPRESSION OF**  
See Pharmacology.

**PARASYMPATHETIC,  
DRUGS FOR STIMULATION OF**  
See Pharmacology.

**PARASYMPATHETIC  
HORMONE**

See Acetylcholine.

**PARASYMPATHETIC SYSTEM**  
See Neurophysiology.

**PARATHORMONE**

The protein hormone of the parathyroid glands which regulates blood calcium, preventing convulsions.

**PARATHYROID**

See also Teeth, Biochemistry Of.

**PARATHYROID  
HORMONE UNITS**

One U.S.P. unit is one-hundredth of the amount of material necessary to raise the Ca level of 100 cc. of blood serum of normal dogs 1 mg. within 16-18 hours.

**PARATHYROTROPIC  
PRINCIPLE**

A hormone of the anterior pituitary which regulates the proliferation of the parathyroid gland cells.

**PAREGORIC**

See Opium.

**PARENCHYMA**

Ground tissue; protoplasm-rich tissue.

**PARIETAL**

Pertaining to a wall or lining.

**PARIETAL EYE**

Pineal body.

**PARIETIC ACID**

See Rhein.

**PARILLIN**

Smilacin;  $C_{26}H_{44}O_{10} \cdot 2\frac{1}{2} H_2O$  questionable; m.p.  $177^\circ$ ; a glycoside of sarsaparilla root consisting of 2 molecules of glucose, rhamnose and parigenin. It is a hemolytic poison even in 10 parts in a million.

**PAROTITIS, EPIDEMIC**

See Mumps.

**PAROTID**

Cheek gland secreting saliva.

**PARRY'S DISEASE**

See Goiter.

**PARTHENOGENESIS**

Development of an unfertilized egg (without male intervention).

**PASSIVE ANAPHYLAXIS**

See Immunological Phenomena.

**PASTEUR ENZYME**

An intracellular catalyst, responsible for the inhibiting action of molecular oxygen on fermentation (Pasteur reaction). According to the photochemical studies of K. G. Stern and associates, the enzyme is a pheohemin protein and closely related to but not identical with Warburg's respiratory ferment. Like the latter, the Pasteur Enzyme reacts with cyanide and with carbon monoxide, besides oxygen. The combination with CO is reversible and dissociated by light.

**PASTEURIZATION**

Heat treatment of milk short of complete sterilization; "holder" method involves 30 minutes at  $150^\circ F$ .

**PASTEUR-MEYERHOF REACTION**

See Pasteur Reaction.

**PASTEUR REACTION**

Pasteur-Meyerhof reaction; the cessation of fermentative processes when anaerobic conditions are removed with replacement by oxidative processes.

**PATHOLOGICAL CHEMISTRY**

See Biochemistry (Definitions).

**PATHOLOGY**

The study of the nature of diseases, and their causes and symptoms.

**PATTEN TEST FOR CYSTINE**

The action of phenyl cyanate on cystine results in the formation of hydantoic acid.

Reference: Zeit. physiol. Chem. 39, 350 (1903).

**PAULY REACTION (1904)**

A not too specific test for tyrosine. A sodium carbonate solution of tyrosine and diazobenzene sulphonic acid gives a red color. Histidine gives a very similar color.

**PAULY REACTION FOR HISTIDINE AND IMIDAZOLE**

The test solution is made alkaline with sodium carbonate and then treated with diazobenzenesulfonic acid. A dye, pure orange in acid and cherry-red in alkaline solution, is produced. Sensitivity — 1:100000.

Reference: Zeit. physiol. Chem. 42, 508; 94, 426; 83, 79.

**PAVOLINI TEST FOR SUGARS**

5 cc. of test solution are shaken with 0.5-1 cc. of alkaline mercuric potassium iodide solution. A yellow or yellow-green precipitate is given by dextrin, fructose, lactose and glucose; sucrose does not

give it.

Reference: Chim. ind. agr. biol. 7, 39 (1931).

**PECTASE**

An enzyme that demethoxylates pectin, yielding pectic acid.

**PECTIC ACID.**

A member of the group of pectins, derived from pectin by demethoxylation.

See Enzymes, Non-Proteolytic.

**PECTIC SUBSTANCES**

See Pectins.

**PECTIN**

A group of substances which consists entirely of a long chain of galacturonic acid units joined 1,4, some of which are esterified with methyl alcohol; water dispersible. In the presence of acids and sugar pectin forms the basis of household jellies.

**PECTINASE**

An enzyme that hydrolyzes pectin to sugars and galacturonic acid. See also Enzymes, Non-Proteolytic.

**PECTINIZATION**

See Pectization.

**PECTINOXANTHIN**

The brilliant red animal xanthophyll of the ovaries of the scallop, Pecten.

**PECTINS**

Complex high molecular weight carbohydrates containing galacturonic acid, galactose, xylose, methanol, acetic acid and possibly arabinose. There are three recognized members: protopectin, pectic acid and pectin, which see.

**PECTIZATION**

An obsolescent word describing the coagulation of sols, and their transformation to gels.

**PECTOSE**

Obsolete name for protopectin.

**PELARGONIDIN**

See Anthocyanins.

**PELARGONIN**

Salvinin; monardin; a glycoside anthocyan of the genarium, consisting of two molecules of glucose and one of pelargonidin. The chloride,  $C_{27}H_{31}O_{15}Cl$  forms scarlet-red needles, water and alcohol soluble.

**PELLAGRA-PREVENTIVE FACTOR**

Nicotinic Acid Amide; the vitamin necessary to prevent pellagra in humans and black tongue in dogs. It is found in buttermilk, beef, yeast, etc. It forms an oxidation-reduction system with its reduced form.

**PELLERIN TEST FOR ADRENALINE IN URINE**

A mixture of 10 cc. urine, 5 cc. saturated aqueous mercuric acetate solution and 1 gm. sodium acetate is vigorously shaken for a minute. The vessel is immersed in a boiling water bath for 10-15 seconds, shaken again, cooled and filtered. A transitory reddish or pink color in the filtrate is positive. Sensitivity—1:200000. Reference: Bull. sci. pharmacol. 33, 204 (1926).

**PELLETIERINE**

$C_8H_{15}N$ ; punicine; alkaloid of pomegranate bark; oil, b.p.  $195^{\circ}$ ; anthelmintic and local anesthetic.

**PELLOTINE**

An alkaloid,  $C_{18}H_{19}O_3N$ ; m.p.,  $110-112^{\circ}$ ; from mescal buttons of Anholonium Williamsii.

**PENICILLIUM**

See Microbiology.

**PENTAMETHYLENETETRAZOLE TESTS**

See Schulte, Zwikker.

**PENTOBARBITAL-SODIUM**

See Nembutal.

**PENTOSANS**

Carbohydrate constituents of gums and mucilages. Have the general formula:  $(C_5H_8O_4)_x$ .

**PENTOSE**

Any monosaccharide with the formula  $C_5H_{10}O_5$ ; with the hexoses make up the most important group of the monosaccharides.

**PENTOSE TESTS, IN URINE, ETC.**

See Bial, Hoffmann, Tauber.

**PENTOSURIA, CHRONIC ESSENTIAL**

See Glycosurias, Non-Diabetic.

**PEONIDIN**

See Anthocyanins.

**PEONIN**

See Paeonin.

**PEPSIN**

A proteolytic and milk-clotting enzyme of the stomach which hydrolyzes all classes of proteins except keratins to proteoses and peptones. With casein its optimum pH is 1.8. It exists in an inactive pre-stage called pepsinogen, formerly thought to be converted to pepsin by  $HCl$ , but since shown to be inactive only because of  $H^+$  concentration. On increasing  $H^+$  concentration activity is brought about.  $i.p.=2.75$ .

**PEPSINOGEN**

See Pepsin.

**PEPSIN, TESTS FOR**

See Jacoby, Kawahara, Solm Reagent.

**PEPSIN, VEGETABLE**

See Papain.

**PEPTIDASES**

Enzymes which attack peptides but not proteins. Their point of attack is at the end of the peptide chain, i.e. at the CONH group, so that they are also called exopeptidases.

**PEPTIDE LINKAGE**

The linkage between the amino group of one molecule of an amino acid with the carboxyl group of another molecule of the same or a different amino acid. This type of linkage builds up proteins.

See Protein Structure.

**PEPTIDES**

In the American classification of proteins, those secondary protein derivatives characterized by being definite compounds of two or more amino acids linked through the amino group of one to the carboxyl of the other. They are not coagulable, and do not necessarily give the biuret reaction. Synthetic peptides are also included in this group.

**PEPTINE RING HYPOTHESIS**

A theory of protein structure based on the postulation of the existence in the protein molecule of piperazine rings with hydrocarbon side chains, and cyclic or heterocyclic rings attached to the side chains.

**PEPTINIZATION**

Graham's word for peptization, now obsolete.

**PEPTIZATION**

The dispersion of a substance to a sol, usually by some added foreign substance.

**PEPTONES**

In the American classification of

proteins, those secondary protein derivatives characterized by being soluble in water, not coagulated by heat, and not being precipitated from solution by saturating their solution with ammonium sulfate.

**PERCORTEN**

A trade name for synthetic deoxycorticosterone acetate.

**PERICARDIUM**

Membrane around the heart.

**PERILLALDEHYDE**

Monocyclic terpene aldehyde; 1-form present in perilla oil.

**PEREIRINE**

An alkaloid,  $C_{20}H_{26}ON_2 \cdot \frac{1}{2}H_2O$ ; m.p.,  $135^\circ$  with decomposition; from bark of *geissospermum vellosii*; used in certain fevers.

**PERIODONTAL TISSUES**

See Teeth, Biochemistry Of.

**PERIPHERAL NERVOUS SYSTEM DRUGS**

See Pharmacology.

**PERIPLOGENIN**

$C_{23}H_{34}O_5$ ; m.p.  $185^\circ$ ; the 3,5,14-trihydroxy aglycone of the cardiac glycoside periplocin.

**PERIPLOCIN**

$C_{30}H_{48}O_{12}$ ; m.p.  $205^\circ$ ; a cardiac glycoside of the bark of *Periploca graeca*, yielding, on hydrolysis, periplogenin, hexose and cymarose; used like digitalis in functional cardiac arrhythmias and pseudo-anginas.

See Digitalis.

**PERITONITIS**

Inflammation of the peritoneum which may be caused by bacterial infection. It may take the forms of (1) acute peritonitis or (2) tuberculous peritonitis. In the first case primary, secondary and postoperative forms are distin-

guished, in the latter, acute and chronic forms. The organism may reach the peritoneum via the blood, lymphatics, by extension of other inflammations, perforation of appendix, stomach, bowel ulcers, hernia, perforations of gall bladder, etc., and postoperative complications. Prophylaxis plays an important role. Parenteral administration of fluid (dextrose and sodium chloride) is used in treatment where nothing can be taken orally.

## PERMEABILITY

Permeability may be defined qualitatively as the readiness with which a dissolved substance penetrates the surface layer or membrane of a phase. In the biological case, with which this article is concerned, the phase is generally a cell. It might, however, be a cell-part—e.g., the nucleus. The readiness of penetration through macroscopic surface layers, such as intestinal epithelium, capillary epithelium, frog skin, etc., is generally considered under this head; but the problem of penetration in those cases is more complex, and will not receive extensive consideration in this place.

The intensity of speed of permeation of any substance is measured by the quantity (in grams, moles, number of molecules, or other units, according to the unit of concentration chosen) which crosses unit area of the surface in unit time. This quantity may be termed the surface current or surface flux. It is generally related linearly to the concentrations of the substance just inside and just outside the membrane. The form of this relationship will be more fully discussed below. **Methods:**

Many different experimental procedures, and empirical "constants" derived from them, have been used in investigating permeability. These may be grouped roughly into direct and indirect methods.

Direct methods are those in which there is, or appears to be, some direct (usually visible) index of concentration changes inside the cell. The use of vital dyes is prominent among such, the intensity of the dye supposedly affording a measure of concentration. Similar procedures, usually applicable only in special cases, are changes in the optical properties (transparency) of the cell cytoplasm which are known to be correlated with changes in content of the substance being investigated. There are two principal and related objections to optical methods. One is that the number of complicating factors—adsorption by heterogeneities in the cytoplasm, effect of pH, diffusion coefficient in the cytoplasm, secondary changes due to specific physiological effects, etc.—makes any clean-cut interpretation of the results in terms of membrane permeability fairly difficult. Only by means of a complete theoretical treatment, involving many difficulties to carry out, could the various side effects be separated from the aim of the investigation—or by a set of additional experiments equally if not more laborious. The second objection is that the relation between the concentration to be determined and the optical effect which is measured is unknown, not necessarily linear, perhaps not even monotonic. Thus, even if permeability could be reliably studied qualitatively by such procedures, they would not, without much



further labor, furnish a quantitative scale.

Indirect methods are principally osmotic. They rely on the fact that cells show visible changes of volume (plasmolysis, etc.) in non-isotonic solutions of substances which do not penetrate them with infinite ease. Thus plasmolysis and its reversal, studied in a time series of observations, may give a measure of rates of penetration. These methods are more usable than the optical ones, and for a long time have been more popular. They are by no means completely free from objection, however. The principal difficulty is that the procedure is likely to produce permeability changes of unknown and perhaps irreversible character. Even more objectionable are methods which frankly capitalize on the production of drastic and irreversible changes in the cell, an example being the use of time required to produce hemolysis of erythrocytes as a measure of permeability. The number of unknown complicating factors here is so excessive as to render this common technique, at least in the reviewer's opinion, a fertile source of error rather than information.

Purely physiological methods, such as those which employ contraction of isolated muscle or the beat of the isolated heart as indices of the penetration of physiologically active substances, are quantitatively useless, and, in view of the fact that most such substances (electrolytes) may conceivably or are known to affect physiological activity without penetrating (e.g., effect of potassium on muscle and nerve), are likely to be qualitatively useless and even misleading as well.

What might be termed indirect physico-chemical methods have centered around measurements of conductivity (of single cells or of cell suspensions). These measurements, if carried out and interpreted with great caution, can be very useful. They are, however, limited to studying electrolytes. They are also open to the possible objection that the method of measurement may induce secondary permeability changes, or damage the cell under investigation.

Undoubtedly the best method theoretically is the direct method of chemical analysis. This is open to the obvious objection that it is quite difficult to carry out. However, a fuller exploitation of the resources of microchemistry than has been customary, and the analysis of large numbers of sufficiently similar cells, should make this method at least feasible. It would seem that the greater expenditure of time and labor would be sufficiently rewarded by reliable results with some quantitative significance.

Naturally, the problem of interpreting such analyses still remains, and much caution is needed. In many cases there is reason to believe that an appreciable part of the substance being studied is not present in the cell free in solution, but bound in some fashion to permanent cell components (e.g., proteins), and probably in some sort of equilibrium with the amount in solution. In such cases analytical results giving total content of the substance in the cell would not be sufficient. The same may hold if the substance is not uniformly distributed through the cell, either by virtue of being involved in cellular metabolism or by reason of heterogeneity of the cell in regard to solubility of the substance. In the



latter case, precipitation methods, which permit distribution of the substance to be studied, would be a valuable auxiliary to straight analysis. In case of binding by the cell matrix, conductivity measurements might reveal the true case, though in some cases they may give fallacious results, (e.g., if the time required to take the measurement is as great as the time required for the measuring current to change the state of binding itself). Obviously an adequate theoretical treatment is needed to assist experimental investigation in such cases.

A brief word may be said regarding the material used, which is by and large extraordinarily stereotyped. Among the most popular types of cells for use in permeability studies are the algae *Valonia* and *Nitella*, because of their convenient size and the rather large amounts of cell sap available for analysis, and the erythrocytes of various species, apparently on account of their ready availability. The highly specialized plant cells are objectionable insofar as they are little capable of furnishing useful information regarding the permeability behavior of most animal cells. The erythrocyte is in the highest degree objectionable because it is so degenerate a cell as scarcely to deserve the name at all. Its metabolism is so faint that phenomena connected with the metabolic activity of the cell are likely to go undetected. The erythrocyte is important enough to be worth studying for itself; but it is highly unlikely that the results will shed any light on the permeability behavior of other more active animal cells. Among the best cells so far used are the ova of various species (e.g., frog, fish,

echinoderm). Steinbach has made ingenious use of the rather plentiful protoplasm in the giant axon of the squid.

Results:

To give a complete account of the various findings on the permeability of different substances for different cells, as well as an adequate critique of their often very dubious reliability, would greatly exceed the scope of this brief review. We content ourselves here with a rough summary.

Experiments on artificial "model" membranes suggest that water-soluble substances in the main are permeable according to the relation between their molecular volume and the pore size of the membrane. Substances soluble in lipids or in lipid solvents, on the other hand, seem to permeate lipid-containing membranes according to their lipid solubility. Lipid solubility, of course, is an exceedingly vague term; and in the literature of permeability it has been employed to cover a multitude of sins. It is indisputable that many cells have surface layers rich in phospholipids, although the evidence here is most convincing for the erythrocyte. But it is not so clear that the speed of penetration of a phospholipid surface necessarily bears a simple relation to solubility in olive oil or ether. Some investigators have attempted to account for the various permeability phenomena of cells by postulating mosaic membranes consisting partially of lipid areas; others, such as Davson and Danielli, have argued for multiple-layer membranes consisting of alternate protein and phospholipid layers.

The studies on artificial membranes are more or less, in the

same not too precise sense, borne out by studies on actual cells. Numerous classes of substances, however, show special properties. Thus many cells show electrolyte permeability which may be regarded as due to the charge of the membrane. Moreover, most animal cells are relatively quite permeable to anions, and relatively impermeable to cations. Cation impermeability is more relative than has been supposed, and much doubt has been thrown on past experiments and hasty conclusions by the careful studies of Steinbach. Still not entirely accounted for, but most probably related to selective binding by cell proteins, is the selective retention of K by some cells, and by Na by others.

Mineral acids and alkalis penetrate far less freely than weak organic acids and bases, and  $\text{NH}_3$  and  $\text{CO}_2$ . It seems possible that the undissociated forms of these compounds may penetrate, while the ions are unable to do so.

Special chemical effects are found among electrolytes. Thus series of cations and anions may be established in the order of permeability, which cannot clearly be related to valence, or even to mass or molecular volume. Attempts have been made to account for these series (see "Hofmeister Series") in terms of the hydration of the ions, but unfortunately no complete quantitative treatment has been carried out. Special ion effects have also been attributed to the influence of the ions on the colloidal state (also, unfortunately, a vague concept) of the surface layer; thus the effects of Ca ions are attributed to the coagulation (and increased density) of the membrane by the ions. Decision on these hypotheses awaits

a more satisfactory theory of the behavior of biocolloids.

Among the external influences which alter permeability, the chief is temperature. It may be said that in general increase of temperature increases permeability. But the temperature coefficients which have been measured vary rather widely, and their interpretation even more widely. Further and much more systematic investigation is required here.

#### Theory:

The various crude and unclear empirical "coefficients" developed from the various indirect methods for studying permeability may be discounted as having no theoretical significance whatever. A better choice, employed by many modern investigators, is that of a permeability coefficient obtained by an extension of Fick's Law of diffusion to diffusion across a membrane. According to this, the surface flux is proportional to the difference of concentrations across the membrane. Thus, if the concentration of a substance just inside the membrane is  $c_1$ , and just outside is  $c_2$ , the surface flux from inside to outside is.

$$1) \quad F = h(c_1 - c_2) .$$

In this formulation,  $h$  is termed the coefficient of permeability. It is assumed to be a function of temperature, but not of concentration of the permeating substance.

For experimental purposes, (1) may be inverted to state that  $h$  is the surface flux divided by the concentration drop across the surface. If these two quantities are experimentally measured,  $h$  is known. The assumed constancy of  $h$  may be checked by making the measurements with various concentrations, within the concentration limits in

which no special effects on the state of the cell are to be expected.

(1) fails to account for any of the forms of selective and anomalous permeability (which, far from anomalous, are very nearly the rule). It is open to objection also from a simple physical consideration. If the penetrating substance does not enter chemical reaction in the cell, its surface flux would be zero in the steady state or at equilibrium. But this gives  $c_1 = c_2$ —that is, the distribution of the solute between cell and external medium is always equal at equilibrium. But this is obvious nonsense; it is not true even for the distribution of a solute between two adjacent non-living solvents, which is accordingly characterized by a partition coefficient or partition ratio, which is unity only in special cases.

One may attempt to make a phenomenological correction by introducing the partition constant  $p$ , the equilibrium value of  $c_1/c_2$ . Thus:

$$1') \quad F = h(c_1 - pc_2).$$

This is free from the objections to (1), although it can as yet be tested only in a purely negative fashion, since values of  $p$  for living systems are not available. But it is easy to obtain essentially the same formula by a kinetic theory derivation, which has the advantage that the assumptions implicit in the formula are clear in advance.

The theory begins by deriving  $F$  for a surface layer without thickness. It is assumed that in general the potential energy of a diffusing molecule of solute, due to intermolecular forces of various sorts, will exhibit a finite difference (or a very sharp if continuous change) at the interface between two dis-

tinct media. It assumes further that there may in addition be an energy barrier at the interface, giving an "activation energy" for the passage of a molecule from one phase to the other, a different activation energy for passage in the reverse direction. It assumes finally that, in a steady state of flow, as distinguished from equilibrium, the distribution of molecular velocities is not Maxwellian, but a modification of the Maxwellian, similar to the one determined by Lorentz for electrons in his theory of conductivity. The introduction of these assumptions into the correct kinetic theory expression for the flux across unit area of the interface gives:

$$2) \quad F = a_1 c_1 - a_2 c_2,$$

where the coefficients, aside from a negligible dependence on  $T^{1/2}$  ( $T$  being the absolute temperature), are primarily exponentially dependent on the "activation energies" divided by  $kT$  ( $k$  the Boltzmann gas constant). (For the complete expressions see the original paper, Reiner 1941.)

If, analogously to (1), we define the permeability as  $F/(c_1 - c_2)$ , it is clear that the result will not in general be independent of concentrations, but only if  $a_1 = a_2$ . But  $a_1$  and  $a_2$  themselves may now be termed coefficients of permeability, and we reconcile ourselves to the fact that it requires two constants instead of only one to describe the relationship of the diffusing solute to the membrane of a given cell.

It is to be noted that these coefficients are functions not only of solute-membrane interaction, but of the interaction of solute with external medium and cell cytoplasm as well. It is of course surprising that anyone ever expected to de-

scribe permeability in terms of solute and membrane alone; but this formulation shows the impossibility clearly.

It is evident from (2) that one may select values of the constants which would give flow against a concentration difference (anomalous permeability). The derivation also gives a common-sense reason for such instances: attractive or repulsive forces acting so as to oppose the kinetic force of a concentration difference. This result suggests that a similar treatment might apply to some of the problems of absorption and "secretion" encountered in the activity of the intestinal epithelium and the kidney tubules.

An extension to membranes of finite thickness gives a formula formally identical with (2), but with more complicated coefficients, and containing the diffusion coefficient of the solute in the membrane, and the membrane thickness. As was to be expected, it reduces to (2) for zero membrane thickness; at no time does one get infinite permeability for zero thickness.

The direct determination of the coefficients requires a series of measurements of  $F$  and the concentrations. These can then be fitted to (2), and the coefficients obtained graphically or by least squares. Independent check of (2) by direct measurements of the energy factors involved, and further elaboration of the theory by assuming explicit forms of the potentials in various special cases, would be highly desirable.

Still unsolved theoretical problems of great interest, in which the formulation of the present theory may be of use, are the relation of permeability changes to cellular

metabolism, to stimulus, and (in ova) to fertilization.

Literature:

E. Gellhorn, "Das Permeabilitätsproblem" (Springer, 1929).

H. Burr Steinbach, "Electrolyte Balance of Animal Cells," Cold Spring Harbor Symposia on Quantitative Biology, VIII, 242-254.

J. M. Reiner, "Diffusion and Biological Membrane Permeability. II.," *Phil. Sci.*, 8, 105-114.

See also *Electrolyte Balance in Muscle*.

JOHN M. REINER

#### PERMEABILITY, PROTOPLASMIC

See Protoplasm.

#### PERMEABILITY, GLYCEROL TYPE

The uneven distribution of a substance in the body on ingestion, as in the case of glycerol, sucrose, sulfate, thiocyanate, chloride.

#### PERMEABILITY, PHYSIOLOGICAL

The permeability of a membrane while physiological processes go on, such as active oxidation.

#### PERMEABILITY, UREA TYPE

The uniform distribution of a substance in the fluids and the cells of a body, as in the case of ingestion of urea or sulfanilamide.

#### PERMIAN

See Paleozoic.

#### PERONNET-TRUHAUT REACTIONS FOR AMINO ACIDS AND URIC ACID

A solution of 0.1 gm. of amino acid in 2 cc. 10% sodium hydroxide solution is stratified with 2 cc. of 0.1% alcoholic m-dinitrobenzene solution; an intense violet ring is formed. The reaction is

given by glycine, lysine and phenylalanine.

Uric acid gives a violet color when treated with 0.1% alcoholic m-dinitrobenzene solution and 1 cc. 10% sodium hydroxide.

Reference: J. pharm. chim. 18, 339 (1933).

## PEROXIDASES

A group of enzymes widely distributed in plant and animal tissues; usually prepared from horseradish; transfer peroxide oxygen to oxidizable substances. The pH range of activity is from 4 to 10, optimum between 5-6. There probably is a reduced heme group in the structure.

## PEROXIDE IN ETHER, TEST FOR

See Stamm.

## PEROXIDE TESTS, IN MILK

See Borinski, Grimmer, Lison.

## PERRIN REACTION FOR INOSITOL

2 drops of the concentrated test solution are evaporated on platinum foil with 1 drop of silver nitrate and ignited. The hot residue has a pale pink color which disappears on cooling and reappears on heating.

Reference: Ann. chim. anal. chim. appli. 1909, 182.

## PERSEITOL

$C_7H_{14}O_7$ ; a heptose alcohol of seeds of species *Persea*, m.p. 188°.

## PERVAPORATION

The evaporation of the dispersions medium from a colloidal system by suspending the liquid in a colloid bag, and heating. If the liquid also contains crystalloids these deposit on the outside of the bag.

## PETIT MAL

See Epilepsy.

## PETTENKOFER TEST FOR BILE ACIDS IN URINE

The addition of sucrose and concentrated sulfuric acid to urine gives rise to an intense red to violet color in the presence of bile acids.

Reference: Ann. Chem. Pharm. 52, 90 (1845). Jahresber. Tierchem. 1892, 539; 1894, 676; Zeit. anal. Chem. 15, 106. J. pharm. chim. 1908, 54.

## PIFFNER-MYERS COLORIMETRIC DETERMINATION OF METHYLGUANIDINE

6 gm. sodium nitroprusside and 8.5 gm. sodium ferrocyanide are dissolved in 100 cc. water; 15-20 minutes before use 1 part of the solution is mixed with 10% sodium hydroxide and 2 parts 3% hydrogen peroxide. 1 cc. of this solution is treated with 4 cc. of the unknown guanidine solution and compared with the color of a standard solution.

Reference. Proc. Soc. Exptl. Biol. Med. 23, 830 (1926).

## pH

A direct measure of acidity or an indirect measure of alkalinity.

Mathematically expressed it is

$$pH = \log \frac{1}{(H^+)}$$

## PHAEOPHORBIDS

See Chlorophyll.

## PHAGE

See Bacteriophage.

## PHAGE-BACTERIUM REACTION

See Bacteriophage.

## PHAGES AND GENES

See Genetics.

## PHAGOCYTE

See Leucocytes.



**PHARBITIN**

Pharbitisin; isoconvolvulin;  $C_{54}H_{96}O_{27}$ ; a glycoside of seeds of *Pharbitis nil*, composed of glucose, rhamnose and ipurolic acid (3:11-dihydroxymyristic); violent cathartic.

**PHARBITISIN**

See Pharbitin.

**PHARMACODYNAMICS**

See Pharmacology.

**PHARMACOGNOSY**

See Pharmacology.

**PHARMACOLOGY**

Pharmacology (Gr. *pharmakon*, drug; *logos*, science) is the science of drugs or medicinal agents. The subject includes the nature, properties, preparation, action and uses of all materials used as medicine. Because of the wide scope of pharmacology it is subdivided into: Pharmacy, which deals with the preparing, compounding and dispensing of drugs; Pharmacognosy, which deals with the physical properties and origin of crude drugs; *Materia Medica*, which is the study of the source, composition, properties, preparation and dose of all medicinal agents; Toxicology, which is the science of poisons; Pharmacodynamics, which is the study of the action of drugs on the living organism; and Therapeutics, which is the application of drugs in disease.

In the development of pharmacology, more and more emphasis has been given to the action of drugs in the organism so that today the term pharmacology is often considered synonymous with pharmacodynamics. Therapeutics has steadily gained ground and has markedly influenced the trend of pharmacology. In the early period

of the science crude plant products and minerals such as calomel, tartar emetic and magnesium sulfate were the important materials of medicine. Then came the isolation of the active ingredients from potent drugs—morphine from opium, atropine from *belladonna*, strychnine from *nux vomica* and quinine from cinchona bark. This was followed by a period in which the introduction of synthetic drugs into therapy was the dominant activity. Chloral hydrate as a soporific, the salicylates as analgesics, procaine as a local anesthetic, cinchophen as an antipodalic are examples. At the turn of the century came the first chemotherapy era with Ehrlich's salvarsan the most outstanding achievement. After a lapse of several decades another intensive period of activity in this field was initiated by the discovery of the effectiveness of prontosil and of sulfanilamide against streptococcal infection. In recent years the hormones and the vitamins have come into the limelight and the study of their pharmacological action is well under way.

The key objective of pharmacology is the study of the action of drugs on the organism. Much information has been acquired by empirical observations, by accidental discoveries, and by planned research. Animal experimentation has been and is still of utmost importance in advancing the science. The correlation of chemical structure and physiological activity is responsible for much of the rapid progress. As soon as it was discovered that sulfanilamide was chemotherapeutically active, its structure became the basis for the synthesis of related compounds such as sulfathiazol, sulfadiazine



and sulfapyridine, which are of even greater therapeutic value.

It is common practice to classify drugs on the basis of the systems on which they act. The central nervous system depressants form a large class, since it includes all the agents capable of producing general anesthesia. Likewise it covers the hypnotics and sedatives as well as the analgesics and the antipyretics. Morphine and the opium alkaloids receive special attention because of their great clinical and theoretical importance. The local anesthetics constitute a separate group. Cocaine and procaine are the most representative members of this class. The stimulants of the central nervous system include the xanthines, strychnine, picrotoxin, metrazol, and coramine.

The drugs acting on the peripheral nervous system constitute an important group which is subdivided into the parasympathetic and the sympathetic. The most important stimulants of the parasympathetic system are acetylcholine, acetyl- $\beta$ -methylcholine, pilocarpine, physostigmine, and prostigmine; the depressants are atrophine, scopolamine, hyoscyamus and their derivatives. The stimulants of the sympathetic system are epinephrine, ephedrine and related compounds.

The cardiovascular drugs because of their great value in therapy occupy an important place in pharmacology. The digitalis group, quinidine and the nitrites are the most important agents under the above heading. The diuretics and the antidiuretics constitute another group. To understand their action a knowledge of water and mineral balance is required.

A group of drugs acting specifically on the gastrointestinal tract is treated as a class and subdivided as follows: emetics, carminatives, bitters, hydrochloric acid, anacids, digestants, cathartics, and anthelmintics.

The oxytocic drugs constitute a small but important group. The principal agents are the ergot alkaloids, quinine and the posterior pituitary hormone. Another group are the drugs acting on the blood forming organs. Iron salts and the antipernicious anemia principles in the form of liver extract and desiccated stomach are the most effective agents. It is to be noted that no successful drugs for the control of the production of leukocytes have been found. Of utmost importance are the drugs used to combat pathogenic microorganisms. The antiseptics and germicides are usually general rather than specific in their action. Among the important specifics are quinine and atabrine in malaria; chaulmoogra oil in leprosy; the arsenicals, bismuth, iodides and mercurials in syphilis; emetin in amebiasis; and the sulfonamides, particularly in streptococcic and other bacterial infections.

The newest chapter in pharmacology deals with vitamins and hormones. Some of the hormones, such as epinephrine and thyroid have, however, occupied a prominent place in pharmacology for many years.

Pharmacology is not an independent science. It draws freely upon physiological chemistry, physiology and the other related branches of science. Its aims are practical rather than theoretical and it is therefore the backbone of thera-

peutics. To pharmacology medicine owes the continuous shift from empirical to a controlled and scientific treatment of disease.

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## PHARMACY

See Pharmacology.

## PELLANDRAL

A terpene aldehyde of water fennel oil, etc.

## PELLANDRENE, ALPHA AND BETA

Monocyclic terpenes; d-alpha occurs in bitter fennel, ginger-grass oils; l-alpha in eucalyptus oils; d-beta in water fennel and lemon oil; l-beta in some peppermint oils.

## PHENACETIN

Aceto-p-phenetidine, an antipyretic and analgesic.

## PHENOBARBITAL

$C_6H_5(C_2H_5)C(CONH)_2CO$ ; phenyl ethyl barbituric acid or phenylethylmalonylurea; used as a hypnotic in nervous insomnia and states of nervous excitement, and as a sedative in epilepsy.

## PHENOBARBITAL TEST

See Ranwez.

## PHENOBARBITONE

See Luminal.

## PHENOGAMS

Plants bearing flowers and seeds.

## PHENOL COEFFICIENT

See Microbiology.

## PHENOL DERIVATIVES, ESTROGENIC ACTIVITY OF

See Estrogens, Synthetic.

## PHENOLPHTHALIN

Phthalin; dihydroxy-triphenylmethane-2-carboxylic acid, m.p. 225°,

a reagent for oxidases, blood, HCN, peroxide.

## PHENOLSULPHONPHTHALEIN TEST

A test of renal function. On a given amount of the phenolsulphophthalein the amount excreted in two hours is determined.

## PHENOTYPIC EFFECTS

See Genetics.

## 1-PHENYLALANINE

$\beta$ -phenyl- $\alpha$ -amino propionic acid;  $C_9H_{11}O_2N$ ; needles or leaves, v.s. hot water, sl. sol. cold, m.p. 283°. i.p. 5.36; an indispensable amino acid found to a large extent in proteins of seeds and young plants.

## PHENYLALANINE METABOLISM

Phenylalanine is mostly converted to tyrosine, whence it is further catabolized. To some extent, particularly in phenylketonuria, it is converted to phenylpyruvic acid. Strongly ketogenic.

## PHENYLALANINE TEST

See Fischer.

## PHENYLGLYCINE TEST

See De Coninck.

## PHENYLKETONURIA

The occurrence of phenylpyruvic acid in the urine, found in certain mentally deficient individuals. The disease is hereditary, traceable to a single recessive Mendelian character.

## PHENYLKETONURIA, HEREDITARY

See Genetics.

## PHENYLPIYRUVIC ACID

$C_6H_5CH_2COCOOH$ ; an intermediate of phenylalanine metabolism, found particularly in phenylketonuria.

**PHENYLPYRUVIC  
OLIGOPHRENIA**

See Phenylketonuria.

**PHILOTHIONE**

An old name for glutathione.

**PHLOBAPHENES**

Inert, insoluble, reddish or brownish, amorphous anhydrides of tannins.

**PHLORHIZIN**

See Phlorizin.

**PHLORIDZIN**

See Phlorizin.

**PHLORIZIN**

Phloridzin; 2-phloretin- $\beta$ -glucoside; asebotin; a glycoside of rosaceae (apple, cherry, pear and plum) consisting of glucose and phloretin. Causes glycosuria, (phlorizin diabetes) on subcutaneous injection by preventing kidneys from reabsorbing glucose and by inhibiting phosphorylation; needles, m.p. 108-9°; used as test for renal insufficiency.

**PHLORIZIN GLYCOSURIA**

See Glycosurias, Non-Diabetic.

**PHLORIZINIZE**

To bring about an artificial diabetic condition by the administration of phlorizin.

**PHLORIZIN TESTS**

See Cremer, Lambrecht.

**PHLOROGLUCINOL**

1:3:5-trihydroxybenzene; found in many glycosides; m.p. 219° anhydrous.

**PHLOROGLUCINOL-HCl TEST**

A test for pentoses depending on the formation of a red color when the sugar is heated with phloroglucinol and HCl.

**pH MEASUREMENT**

The most wide-spread method is

the glass electrode, which relies on empirical correlation with the hydrogen electrode, good to 0.01 pH; the quinhydrone electrode is subject to many errors, as salt and protein effects; and colorimetric methods are limited by the sensitivity of the color reaction used.

**$\beta$ -PHOCOECOLIC ACID**

$C_{24}H_{40}O_5$ ; m.p. 222°. A bile acid found in the seal and walrus. It is 3,7,23-trihydroxy cholanolic acid.

**PHORBIN**

See Chlorophyll.

**PHOSPHAGEN**

Phosphocreatine; the compound, which on breaking down to creatine and phosphoric acid, provides the energy of muscle contraction. It is resynthesized. The term is sometimes confused with arginine phosphate in the discussion of invertebrate muscle.

**PHOSPHATASES**

A group of widely distributed esterases, important in bone formation, muscle activity, and lactation. They hydrolyze nucleic acids and phosphoric acid compounds of fats, proteins, carbohydrates, amino acids, etc. Rickets is accompanied by a high serum phosphatase.

See also Enzymes, Non-Proteolytic.

**PHOSPHATE BOND ENERGY**

A general interrelationship between phosphate metabolism and energy supply has become increasingly apparent through the growing understanding of muscle chemistry. Therewith, phosphorylation of organic compounds which occurs during metabolic processes became of new significance. First, it was found that the phospho-creatine bond served as a reservoir of con-

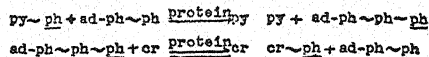
traction energy.<sup>1</sup> This discovery was followed soon by the isolation of a number of unusual compounds: adenosinepolyposphate, phosphopyruvate and lately of the carboxyl-phosphates.<sup>2</sup> These compounds, like creatinephosphate, contain energy condensed in phosphate bonds which although differing in chemistry appear to be equivalent in energy content. The average derivable from hydrolytic decomposition of these energy-rich phosphate bonds is 11,000 cal.

This group of compounds has to be distinguished clearly from the ordinary phosphate esters:<sup>3</sup> glycerol-, hexose-phosphate, phosphoglycerates and the other compounds where, in ordinary ester linkage, phosphate is linked to an alcoholic hydroxyl. The ordinary ester linkage has an average energy of only 3000 cal.<sup>3</sup> The symbol  $\sim\text{ph}$  has been assigned to the energy-rich bond and  $-\text{ph}$  to the ordinary ester bond.

The 11,000 cal. condensed in the energy-rich phosphate bond,  $\sim\text{ph}$ , represent a biological energy-unit. Migrating continuously from compound to compound the quantity  $\sim\text{ph}$  in many respects can be regarded as largely independent of the compound to which it is attached. The distribution of this unit is handled by a special pooling and transfer system, the adenylic acid system. The delivery of  $\sim\text{ph}$  to and from this system occurs on compound-specific enzymes.

In these transfer reactions adenylic acid fulfills the double function of a prosthetic group, and of a carrier between the enzymes. A transfer of  $\sim\text{ph}$ , e.g. from phosphopyruvate ( $\text{py}\sim\text{ph}$ ) to creatine ( $\text{cr}$ ), may thus be formulated as

follows:<sup>4</sup>



At the present time reaction (1) seems in this particular case irreversible. Reaction (2) is easily reversible.

One mol of adenylic acid can accommodate a maximum of two  $\sim\text{ph}$ :

The first phosphate in ATP (Adenosine-Tri-Phosphate, adenylypyrophosphate) is an ordinary ester phosphate. The two end-phosphates are bound in energy-rich pyrophosphate linkage (Lohmann's formula):<sup>5</sup>

Probably only the terminal  $\sim\text{ph}$  is used directly and the shuttling of  $\sim\text{ph}$  is facilitated through alternating phosphorylation of ADP (adenosine-di-phosphate) and dephosphorylation of ATP.<sup>6</sup>

The enzymatic mechanism of phosphate transfer resembles very closely that of hydrogen transfer. Generally, phosphorylation-dephosphorylation systems are comparable to hydrogenation-dehydrogenation systems. Such resemblance is not merely superficial. As an O/R potential is assigned to a hydrogenation system, a phosphate group potential may be assigned to a phosphorylation-dephosphorylation system. The phosphate group potential<sup>3</sup> is measured adequately through the energy liberated by dephosphorylation.

When the biological important phosphate derivatives are grouped according to bond energies, there is an aggregation around two levels of potential: (1) the 11,000 cal. level of the energy-rich bond and (2) the 3000 cal. level of the

ordinary ester bond. The free inorganic phosphate is at zero level on the base line of our scale.

Phosphate bond	Average group potential calg.
Energy-rich, ~ph	11,000
Ester, -ph	3,000
Inorganic ph	0

The relative level of potential of two phosphate bonds indicates the direction of energetically possible phosphate transfer, in the same manner as the relative O/R potential level indicates the possible direction of hydrogen transfer. It appears thus from Table I that the phosphate in energy-rich bond never can originate from, but may be used to form ester bonds. The compound with energy-rich bond is frequently a phosphate donor to alcoholic hydroxyl, the phosphate acceptor. Indeed, formation of phosphate ester bonds in cell constituents such as nucleic acid, lecithine, etc. is an important function of energy-rich phosphate.

#### Metabolic Generation of Phosphate Bond Energy

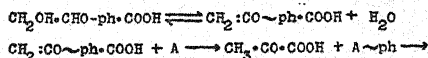
To supply the cell with energy, the energy unit ~ph is continuously generated through a repeating sequence of metabolic reaction phases:

- (1) Organic fixation of free phosphate.
- (2) The development of the energy "hump" of the energy-rich bond.
- (3) Delivery of ~ph to the adenylic acid system (A).
- (4) Eventual release of free phosphate through utilization and reentrance to phase (1), etc.

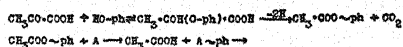
Two of the mechanisms which develop the ~ph-hump are under-

stood at the present time. These are:

#### (1) Dehydration of ph-2-glyceric acid to ph~enol-pyruvic acid:<sup>1</sup>



(2) Dehydrogenation of a carbonyl-phosphate addition product to carboxyl~phosphate, as in dehydrogenation of pyruvic acid to acetyl phosphate and CO<sub>2</sub>:<sup>3</sup>



This passage of phosphate through metabolic cycles as a vehicle for energy explains its metabolic indispensability and that of adenylic acid.

#### Utilization of Phosphate Bond Energy

When the metabolically generated ~ph reaches the adenylic acid pool, it becomes available for utilization. The following examples illustrate how phosphate bond energy is used for general purposes of the organism.

(1) Phosphate bond energy enables the organism to deposit glucose as glycogen.<sup>7</sup> Energy has to be expended in this reaction because the glucose bound in glycogen is on a higher energy level than free glucose. The energy difference is equal to that between free and bound phosphate. The procedure adopted by the cell is first to combine glucose with phosphate by using the energy drop from adenylic ~ph to glucose ester-ph. Subsequently the phosphate in glucose-phosphate is exchanged for glucose thus building up the polysaccharide structure. The following sequence of reactions occurs:



A~ph + glucose

↓  
ph-6-glucose

↕  
ph-1-glucose

↕  
glycogen + ph

The first step is accompanied by a loss of 8,000 cal. because of the conversion of energy-rich ~ph into energy-poor-ph. This step therefore is irreversible. The subsequent steps are all reversible. The last step, in upwards direction, is frequently referred to as phosphorylation of glycogen and is of importance as one of the few reactions allowing the entrance of free phosphate into organic bond.

(2) Phosphate bond energy is utilizable for transformation of fructose into glucose.<sup>8</sup> An enzymatic interconversion of the sugars occurs easily, provided they are phosphorylated. Therefore, in order to convert fructose into the metabolically more valuable glucose, the energy of one ~ph is expended to phosphorylate the fructose:

A~ph + fructose

↓  
ph-6-fructose

↕  
ph-6-glucose

↓  
glucose + phosphate

These examples are a first and precious insight into the mechanics of an energy utilization in living organisms.

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# BIBLIOGRAPHY

- <sup>1</sup> C. H. Fiske and Y. Subbarow, *J. Biol. Chem.*, 81: 629 (1929).
- P. Eggleton and G. P. Eggleton, *Biochem. J.*, 21: 190 (1927).
- O. Meyerhof and J. Suranyi, *Biochem. Z.*, 191: 106 (1927).
- <sup>2</sup> O. Warburg and W. Christian, *Biochem. Z.*, 303: 40 (1939).
- F. Lipmann, *J. Biol. Chem.*, 134: 463 (1940).
- <sup>3</sup> F. Lipmann, *Advances in Enzymology*, 1: 99 (1941).
- <sup>4</sup> J. K. Parnas, P. Ostern and T. Mann, *Biochem. Z.*, 272: 64 (1934).
- <sup>5</sup> K. Lohmann, *Biochem. Z.*, 282: 120 (1935).
- <sup>6</sup> H. M. Kalckar, *J. Biol. Chem.*, 143: 299 (1942); *Chem. Rev.* 28, 71 (1941).
- <sup>7</sup> C. F. Cori, *Cold Spring Harbor Symposium*, 7: 260 (1939).
- S. P. Colowick and E. W. Sutherland, *J. Biol. Chem.*, 144: 423 (1942).
- <sup>8</sup> C. F. Cori and W. M. Shine, *J. Biol. Chem.* 114, XXI (1936).
- T. Goda, *Biochem. Z.*, 297: 134 (1938).

## PHOSPHATE GROUP POTENTIAL

See Phosphate Bond Energy.

## PHOSPHATE METABOLISM

See Phosphate Bond Energy.

## PHOSPHATIDES

Phospholipids.

## PHOSPHOARGININE

A phosphate of arginine which takes the place of phosphagen in invertebrate tissue.

## PHOSPHOCREATINE

See Phosphagen.

## PHOSPHODIESTERASES

See Enzymes, Non-Proteolytic.

## PHOSPHOGLUCONIC ENZYME

The pyridinoprotein enzyme containing coenzyme II, which catalyzes the oxidation of 6-phosphogluconate to its ketonic acid. Found in yeast and animal tissues.



**PHOSPHOLIPIDS**

Compound lipids containing phosphoric acid and nitrogen; as lecithin, cephalin, sphingomyelin.

**PHOSPHOMONOESTERASES**

See Enzymes, Non-Proteolytic.

**PHOSPHOPROTEINS**

In the American classification of proteins, the phosphoproteins are conjugated proteins, in which orthophosphoric acid is esterified with the hydroxy group of a hydroxy amino acid, especially serine. Example: Casein.

**PHOSPHOPYRUVATE**

See Phosphate Bond Energy.

**PHOSPHOROLYSIS  
(OF GLYCOGEN)**

See Phosphate Bond Energy.

**PHOSPHORUS METABOLISM**

See Teeth, Biochemistry of.

**PHOSPHORYLASE**

See Enzymes, Non-Proteolytic.

**PHOSPHOTIDIC ACIDS**

Diglyceride phosphoric acids.

**PHOTOGEN**

See Bioluminescence.

**PHOTOMETER**

An instrument which measures the intensity of light.

**PHOTOTROPISM**

Reaction of a living form to light.

**PHOTOSYNTHESIS**

The term photosynthesis might be applied to any synthetic process dependent upon radiant energy. Common usage of the term by plant scientists to denote the assimilation of carbon dioxide by green plants under the influence of light, has resulted in fairly general acceptance of this more limited meaning. Assimilation of carbon dioxide by organisms other than green plants,

such as algae of various colors, and certain classes of bacteria, is also called photosynthesis, provided the energy required for assimilation is supplied by absorbed radiation, whether visible or not. Certain groups of organisms assimilate carbon dioxide by mechanisms which derive the necessary energy from chemical reactions, rather than from absorbed radiation. This type of metabolism is called chemosynthesis, and is not included under photosynthesis. For example, the colorless sulfur bacteria (Thiobacteria) oxidize compounds of sulfur or elementary sulfur, and utilize the energy set free by this oxidation to assimilate carbon dioxide. No irradiation is required, apart from the maintenance of physiological temperatures. These sulfur bacteria are classed as chemosynthetic. Certain other sulfur bacteria (Thiorhodaceae) also oxidize compounds of sulfur or elementary sulfur in connection with carbon dioxide assimilation, but the assimilatory process is dependent upon the absorption of radiation, either visible or infrared. These organisms are classed as photosynthetic.

Most of the organisms capable of photosynthesis are classified in the plant kingdom, and the subject has therefore been regarded as belonging to the science of botany. But a number of outstanding contributions to our knowledge of photosynthesis have come from investigators primarily interested in fields other than botany, notably chemistry and physics. The photosynthetic process presents certain problems which have frequently been overlooked by botanists and plant physiologists, but which have excited the interest of outstanding chemists and physicists.

Prior to the beginning of the nineteenth century, it was believed that the carbon content of plants in general was derived from the humus of the soil. Indeed this belief is to be found in text books of plant physiology up to 1839, although more than a century earlier the Dutch iatro-chemist van Helmont had reported an experiment which should have sufficed to refute the humus theory of plant nutrition. van Helmont planted a willow cutting in a tub of soil, and watered it with rain water for a period of about 2 years. During this time the dry weight of the soil decreased only 2 ounces, while the willow gained in weight about 160 pounds. Knowledge of chemistry and the nature of matter was so limited in van Helmont's time that correct interpretation of this remarkable experiment had to wait until a later date. An understanding of the nature and significance of photosynthesis developed in the latter part of the eighteenth and early nineteenth centuries, coincident with the rejection of the phlogiston theory of combustion as a result of the work of Priestly, Scheele, Lavoisier, and others. Early studies of combustion stimulated an interest in the gas exchange of plants and animals, and it was established by Ingen-Housz that in light the green parts of plants produced a gas (oxygen) which would support combustion, as well as the life of small animals. He recognized that in darkness plants absorbed oxygen, and that the non-green parts absorbed oxygen in both light and darkness. de Saussure carried out more precise experiments on the gas exchange of plants, and gave an account of the process of photosynthesis which was later published

as one of Ostwald's *Klassiker der Exakten Wissenschaften*. This account includes most of the fundamental facts concerning photosynthesis which are recognized today.

The botanists of the nineteenth century made but few advances beyond the achievements of de Saussure although the dependence of photosynthesis on various external factors was given a good deal of attention. It was observed that the photosynthetic activity of various organisms depended upon the light intensity, the temperature, and the carbon dioxide concentration, but the results of different workers were often in wide disagreement, and no systematic understanding of the significance of these factors was developed until after 1900, when F. F. Blackman showed that the influence of any one factor on rate of photosynthesis depended on the concentration or intensity of the other factors. Blackman found that temperature changes were almost without effect on the rate of photosynthesis if the light intensity was low, but that high light intensities resulted in a marked dependence of the rate on temperature. He formulated a general statement of the results of his work, known as the theory of optima and limiting factors, and this theory exerted a strong directive influence upon subsequent work, because it was clear that the study of the dependence of photosynthesis upon any one factor was significant only if other factors also were controlled. But the most important result of Blackman's work was the recognition that two types of reaction are involved in the process of photosynthesis, and that the characteristics of these different reactions may be studied separately by proper adjust-

ment of the experimental conditions. Thus at low light intensities, the rate of the process is limited by the photochemical steps, which are not dependent on temperature, while at high light intensities the photochemical steps are completed so rapidly that they are no longer rate-limiting, and the rate of the process is limited by the chemical steps, which have a high temperature coefficient. The chemical steps are called collectively the Blackman reaction.

Warburg and Negelein made a careful study of the characteristics of the Blackman and photochemical reactions, by working at high and low light intensities, with the unicellular green alga, *Chlorella pyrenoidosa*. Their work has become a classic in this field. Among other things, they noted that at high light intensities, when the rate was limited by the Blackman reaction, intermittent periods of light and darkness gave a higher yield of photosynthesis than the same duration of illumination given continuously.

Later work with intermittent light, with more elaborate methods, has shown that it is a valuable means of separating the Blackman and photochemical reactions. The photochemical steps take place only during the light flashes, which may be made so short in comparison with the dark periods that the slower processes of the Blackman reaction proceed only to a negligible extent during the light flashes. The Blackman reaction runs its course during the intervening dark periods, and some of its properties have been revealed by measurements in intermittent light. In this way the average time required for completion of the dark

processes has been estimated to be between 0.01 and 0.02 seconds, at a temperature of 25° C. From measurements of the maximum rate of photosynthesis in continuous light, it has been calculated that per molecule of chlorophyll present, one molecule of carbon dioxide is reduced every 20 seconds. At maximum photosynthesis, the rate is supposed to be limited by the Blackman reaction, so it may seem surprising that the time for this process calculated from the flashing light experiments should be so different from that calculated on the basis of the measurements in continuous light. Very likely several processes are involved in the Blackman reaction, and they may require different lengths of time for completion. But in any case the above comparison is not strictly admissible, because in the flashing light we estimated the time of the Blackman reaction from the maximum number of carbon dioxide molecules reduced per flash, and in the continuous light we based the calculation on the maximum number of carbon dioxide molecules reduced per chlorophyll molecule.

We do not know how many chlorophyll molecules may take part in the reduction of a single molecule of carbon dioxide, but calculations have been made from the flashing light experiments which show that with light flashes so bright that increased intensity causes no increase in photosynthesis, and with dark intervals long enough so that the Blackman reaction can run to completion between each pair of light flashes, the maximum number of carbon dioxide molecules which can be reduced per flash is only about 1/2500th of the number of chlorophyll molecules present.

From thermodynamic considerations we are sure that more than one quantum of light must be absorbed per molecule of carbon dioxide reduced. Measurements indicate that under conditions of maximum photosynthetic efficiency, about 10 quanta of light must be absorbed per molecule of carbon dioxide reduced. We may be quite sure that all these 10 quanta need not be absorbed by the same chlorophyll molecule in order to reduce a particular carbon dioxide molecule, for if this were so the rate of photosynthesis at low light intensities would vary as a higher power of the light intensity. Actually, the rate of photosynthesis at low intensities varies as the first power of light intensity. But no fully satisfactory explanation has yet been given of the manner in which the absorption of the 10 quanta of light are distributed among the 2500-odd chlorophyll molecules which appear to be present per molecule of carbon dioxide reduced per flash. Since the 10 quanta do not provide much of a margin of energy for the reduction of carbon dioxide to carbohydrate, there is not room for any large proportion of ineffective absorptions, so it appears that the assimilatory mechanism must have some provision for bringing the energy absorbed by widely separated chlorophyll molecules to act in the reduction of a single carbon dioxide molecule. Probably the interpretation of these basic observations will require the best ingenuity of physical chemists.

The attention devoted to the kinetics of photosynthesis is partly the result of failure to develop a more constructive angle of attack. While much has been learned about the

chemistry of other physiological processes from experiments with ground cells and cell extracts, and from the introduction of supposed intermediate substances, such lines of attack have so far been quite unsuccessful in the study of photosynthesis. The least disturbance in the cell, such as pricking the membrane with a needle, causes complete cessation of photosynthetic activity. None of the organic substances tested have shown evidence of acting as intermediates in photosynthesis. Substances have either proved to be toxic, or have been first oxidized by the cell to carbon dioxide and water before being built into carbohydrates. We do not know the first substance with which carbon dioxide combines after entering the cell, nor the immediate precursor of carbohydrate. It is also uncertain whether starch or sugar is the first product of photosynthesis, or if there is any single first product of photosynthesis.

Regarding the general nature of the photosynthetic process, our views are probably narrowed by the tendency to regard the process as essentially a synthesis of carbohydrate material. This is because the over-all ratio of exchange of oxygen and carbon dioxide is equal to unity, indicating carbohydrate synthesis.

Since most of the material of average plants is of the same level of reduction as carbohydrate, this ratio is to be expected, but it is quite possible that products both more and less reduced than carbohydrate are also produced in photosynthesis, and that the average exchange misleads us into regarding the entire process as carbohydrate synthesis.

Chemists have long recognized the probability that so profound a change as the synthesis of carbohydrate from carbon dioxide and water must take place in small intermediate steps. There has been much speculation concerning substances of 2 or 3 carbon atoms, as possible intermediates in the process, but there has been no good experimental evidence to support any of the theories advanced. Recent experiments with radioactive isotopes of carbon have indicated that carbon dioxide is probably added as a carboxyl group to pre-existing compounds of high molecular weight (about 1000), and that reduction of the carboxyl group follows. The present view is that this is a more probable mechanism for the synthesis of compounds of high molecular weight than the polymerization of such reduction products as formaldehyde or formic acid, or other compounds of small molecular weight.

However, it has been found that a large number of organisms have the ability to fix carbon dioxide as carboxyl groups on certain carbon compounds, and it is not yet clear that this characteristic of photosynthetic organisms is a part of the photosynthetic mechanism proper.

Experiments with purple bacteria have provided evidence for regarding carbon dioxide assimilation as primarily a process of hydrogen transfer from some hydrogen donor to carbon dioxide, rather than as a removal of oxygen from carbon dioxide and the addition of water. In the case of green plants, the hydrogen donor is water, and oxygen is evolved. In the case of the purple sulfur bacteria, hydrogen sulfide may be the hydrogen donor, and sulfur instead of oxygen is pro-

duced. Certain purple bacteria can also use fatty acids or molecular hydrogen as hydrogen donor. Ordinarily green plants appear to be incapable of obtaining hydrogen from other sources than water, and oxygen is always produced. But it has been shown that certain unicellular algae can use molecular hydrogen for carbon dioxide reduction, provided they have first been kept for some time under anaerobic conditions.

Experiments with a heavy isotope of oxygen support the opinion that the oxygen evolved in photosynthesis comes from water, and not from carbon dioxide.

In higher green plants, the seat of photosynthetic activity is the plastid. The bacteria, and certain algae, do not have plastids but have their light absorbing pigments distributed throughout the cells. The need for a light absorbing pigment is obvious, since neither carbon dioxide nor water absorb visible light or the near infrared. The activity of the chlorophyll in green plants seems to be limited to the spectral region from about 400 to about 700 m $\mu$ . Photosynthetic bacteria carry on carbon dioxide assimilation in the near infrared, as well as in the visible spectrum.

Chlorophyll is apparently responsible for most of the photosynthetic activity of green plants, but there is evidence that the carotenoid pigments which always accompany chlorophyll may play some photochemical part in carbon dioxide assimilation. The red pigment of certain purple bacteria, evidently a carotenoid type of pigment, shows definite photosynthetic activity. The purple bacteria, and also the green



bacteria, have a green pigment akin to chlorophyll, bacteriochlorophyll.

Evidence concerning the activity of accessory pigments is drawn largely from measurements of photosynthetic efficiency in different wave lengths. These measurements are compared with the estimated absorption of the different pigments, based on measurements with extracted pigments. The absorption spectra of the pigments are altered more or less by extraction, so it is impossible to be sure just how the absorption is divided among the various pigments in the living cells. This introduces an uncertainty in the reasoning concerning the activity of accessory pigments, but the evidence is pretty clear in some cases at least.

In recent years the fluorescence of chlorophyll has been studied in order to obtain evidence concerning the mechanism of photosynthesis. Since chlorophyll always fluoresces red, whether it is excited by blue, green, or yellow light, it is believed that the emission of fluorescence indicates it has been raised to an energy level of a certain stability, and that this energy level is the one required for photosynthetic activity. It is not believed that the higher excitation produced by shorter wave lengths can make any more energy available for photosynthesis. Many attempts have been made to correlate the fluctuations in chlorophyll fluorescence with the rise and fall of photosynthetic activity. No certain conclusions can be drawn from this work as yet.

There have been a number of reports of artificial photosynthesis, but these claims have not been substantiated, and it appears that green plants are unique in their ability to reduce carbon dioxide with visible

light. The energy provided by a single quantum of red light is too small for the reduction of carbon dioxide to carbohydrate. The process must be carried out by elementary steps of small enough energy requirements so that a single quantum of red light suffices for each elementary step. At the present time this is the feature of photosynthesis which especially attracts the interest of physicists and physical chemists.

The more important photosynthetic organisms are of course the crop plants and timber trees upon which our civilization depends. These organisms are not adapted to precise quantitative experiments on the nature of the photosynthetic process. Most of our precise knowledge has come from studies on unicellular algae and bacteria. It is to be hoped that when our understanding of the fundamental processes is sufficiently advanced, it will prove to be of value in connection with larger human problems. There has been much study of photosynthesis under natural conditions, and some efforts have been made to correlate the knowledge gained from more precise studies with the behavior of plants under field conditions. Progress in this direction has been very limited, partly because the fundamentals are not yet clearly understood, and partly because clear-cut objectives for field work on photosynthesis have yet to be formulated.

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#### LEADING LITERATURE REFERENCES

Blackman, F. F. Optima and Limiting Factors. *Annals of Botany*, 19: 281-295, 1905.



Emerson, Robert and C. M. Lewis. Carbon dioxide exchange and the Measurement of the Quantum Yield of Photosynthesis. *American Journal of Botany*, 28: 789-804, 1941.

Franck, J. and H. Gaffron. Photosynthesis: Facts and Interpretations. *Advances in Enzymology*, 1: 199-262, 1941.

van Helmont, John Baptista. *Oriatrike, or Physik Refind.* Translated by J. C. Sometime of M. H. Oxon. Printed for Lodowick Loyd, Cornhill, London, 1662. Chapter XVIII, par. 30, p. 109.

van Niel, C. B. The Bacterial Photosyntheses, and their Importance for the General Problem of Photosynthesis. *Advances in Enzymology*, 1: 263-328, 1941.

Ruben, S. and M. D. Kamen. Photosynthesis with Radioactive Carbon. IV. Molecular Weight of the Intermediate Products and a Tentative Theory of Photosynthesis. *Journal of the American Chemical Society*, 62: 3451-3455, 1940.

de Saussure, T. *Chemische Untersuchungen über die Vegetation* (1804). *Ostwald's Klassiker der Exakten Wissenschaften*, Nr. 15. W. Engelmann, Leipzig, 1890.

Spoehr, H. A. Chemical Aspects of Photosynthesis. *Annual Review of Biochemistry*, 2: 453-470, 1933.

Warburg, O. Über die katalytischen Wirkungen der lebendigen Substanzen. Julius Springer, Berlin, 1928. Part II, Kohlensäureassimilation und Nitrat-assimilation, p. 287-497.

Willstätter, R. and A. Stoll. *Untersuchungen über die Assimilation der Kohlensäure.* Julius Springer, Berlin, 1918.

## PHOTOTROPISM

See Plant Growth Hormones.

## PHRENIC NERVES

See Respiration.

## PHRENOSIN(E)

Cerebron;  $C_{48}H_{98}O_9N$ ; m.p.  $212^{\circ}$ ; a cerebroside whose fatty acid is cerebrononic acid.

## PHRENOSINIC ACID

See Cerebrononic Acid.

## PHTHALIN

See Phenolphthalin.

## PHTHIOCEROL

$C_{84}H_{67}(OH)_2OCH_3$ ; an optically active alcohol typical for human tuberculosis bacteria.

## PHTHIOCOL

2-methyl-3-hydroxy-1, 4-naphthoquinone; a yellow pigment of human tubercle bacilli that has strong anti-hemorrhagic powers.

## PHTHIOIC ACID

$C_{26}H_{52}O_2$ ; a saturated branched-chain fatty acid found in the tubercle bacillus, active biologically in producing tubercular tissue on injection.

## PHYCOCYAN

A chromoprotein found in sea algae.

## PHYCOERYTHRIN

A chromoprotein found in sea algae.

## PHYCOMYCETES

See Microbiology.

## PHOSPHORYLATION

See Phosphate Bond Energy, Carbohydrate Metabolism.

## PHYCOPHAEN

Pigment of brown sea weeds.

## PHYLLOCALINE

See Plant Growth Hormones, Phytohormones.

## PHYLOGENY

The study of the ancestral history of organisms.

## PHYONE

See Growth Hormone.

## PHYSALIEN

Physalin; zeaxanthin dipalmitate;  $C_{72}H_{116}O_4$ ; m.p.  $99^{\circ}$ ; a carotenoid found in fruits of *Physalis alkekengi* and other members of the species. Its structure is  $\beta$ - $\beta'$ -carotene-3-3'-dioldipalmitate.

**PHYSALIN**

See Physalien.

**PHYSETOLEIC ACID**

A 16 carbon, one double bond, unsaturated fatty acid, found in Caspian seal oil.

**PHYSIOLOGICAL ANTAGONISTS**

Physiological antidotes or antidotes which merely mask the symptoms, e.g. atropine vs. morphine, chloroform vs. strychnine, barbiturates vs. cocaine, picrotoxin vs. hypnotics.

**PHYSIOLOGICAL CHEMISTRY**

See Biochemistry (Definitions).

**PHYSIOLOGY**

The study of the functions of organisms.

**PHYSIOLOGY, DEVELOPMENTAL**

A branch of physiology dealing with experimental embryology and chemical embryology.

**PHYSOSTIGMINE**

See Eserine.

**PHYTASE**

See Enzymes, Non-Proteolytic.

**PHYTIN**

Calcium magnesium salt of phytic acid (inositol hexaphosphoric acid); derived from numerous seeds and grains; used in neurasthenia, anemia, tuberculosis.

**PHYTOCHEMISTRY**

See Biochemistry (Definitions).

**PHYTOHORMONES**

Plant growth hormones; include the auxins (cyclopentene derivatives), heteroauxin (indole-3-acetic acid) and more or less unidentified factors, traumatic acid, caulocaline (stems), phyllocaline (leaves) and rhizocaline (roots). See Plant Growth Hormones.

**PHYTOKINASE**

A papain activator found in papain preparations. It is a polypeptide composed largely of glutamic acid and cystine.

**PHYTOL**

$C_{20}H_{40}O$ ; b.p. 202.5-204° at 10 mm.; diterpenic alcohol produced by the action of alkali on chlorophyll.

**PHYTOMELIN**

See Rutin.

**PHYTOSTEROLS**

Sterols found in plants, e.g. sitosterol, stigmasterol, (q.v.); white solids, optically active.

**PHYTOSTEROL TESTS**

See Kreis, Liebermann.

**PHYCOXANTHIN**

Yellow pigment of diatoms.

**PICRAMIC ACID**

4, 6-dinitro-2-aminophenol, m.p. 169°, a reagent for albumin.

**PICROACONITINE**

An alkaloid,  $C_{32}H_{45}O_{10}N$ , from the tuber of *Aconitum napellus*; m.p., 150°; used as cardiac sedative.

**PICROCROCIN**

Saffron-bitter;  $C_{16}H_{26}O_7$ ; m.p. 154-156°; glucoside of safranal, a carotenoid aldehyde, which is a female determining factor in certain algae, or a gamone (q.v.); used as an abortive.

**PICROLONIC ACID**

1-(p-nitrophenyl)-3-methyl-4-nitropyrazolon, m.p. 116-117°, a reagent for alkaloids, tryptophan, phenylalanin and calcium; also used in forming crystalline derivatives of amino acids for purification.

**PICROTOXIN**

Cocculin, an amaroid,  $C_{80}H_{34}O_{18}$ ; an equimolecular compound of

picrotin and picrotoxinin; m.p., 200°; from berries of various species of coccullus; used as anti-hidrotic.

See Pharmacology.

**PIGMENTATION, HEREDITARY**

See Genetics.

**PIGMENTOBLASTS**

See Hair.

**PIGMENTS, ACCESSORY**

See Photosynthesis.

**PILOCARPINE**

$C_{11}H_{16}O_2N_2$ , m.p. 34°, alkaloid of Jaborandi species, causes profuse perspiration, slows heart beat; antidote to belladonna, stimulant for hair growth.

**PINEAL PRINCIPLE**

A hormone of the pineal gland which causes tadpoles to become transparent and produces sexually precocious dwarfs on injection in successive generations.

**PINITOL**

Matezite; sennite; methyl ether of inositol found in senna, conferrin.

**PINNAGLOBULIN**

Brown respiratory pigment containing manganese, in blood of lamellibranch, Pinna squamosa.

**PINOCAMPHEOL**

Secondary alcohol derived from pinene; l-form in oil of hyssop.

**PINOCAMPHONE**

A dicyclic ketone; l-form found in oil of hyssop.

**PINOCARVEOL**

A dicyclic terpene alcohol of Eucalyptus globulus.

**PINOCYTOSIS**

The incupping of surfaces of single cells due to disturbances of permeability.

**PINWORM**

See Worms, Intestinal.

**PIOTROWSKI REACTION**

See Biuret Reaction.

**PIPERAZIDINE**

See Piperazine.

**PIPERAZINE**

$C_4H_{10}N_2$ ; piperazidine; arthriticin; dispermin; hexahydropyrazine; diethylene diamine; used for gout and rheumatism, and to dissolve urinary stones; m.p. 105-106°, forms hydrate.

**PIPERIDINE**

An alkaloid, hexahydropyridine,  $C_5H_{11}N$ ; m.p., 9°; b.p., 105-106°; from black pepper; is a strong base.

**PIPERINE**

$C_{17}H_{19}O_3N$ ; piperoylpiperide, monoclinic needles from alc. m.p. 128-129.5°. Pungent mildly irritative alkaloid of Piper Nigrum, has pepper-like taste. Synthesized from piperoyl chloride and piperidine. Forms periodide;  $B_2HI.I_2$ , steel-blue needles m.p. 145°.

**PIPERITOL**

A secondary terpene alcohol; l-form found in eucalyptus oils; d-form in a species of Andropogon.

**PIPERITONE**

A terpene ketone; l-form found in eucalyptus oils; d-form in Japanese peppermint; camphor-like odor.

**PIPERONAL**

Heliotropin; piperonylaldehyde; m.p. 37°,  $C_8H_6O_3$ , found with vanillin; a perfume also used as a pediculicide.

**PITAYINE**

See Quinidine.

**PITOCIN**

An aq. soln. containing the oxy-

totic principle from the pituitary gland, posterior lobe; used to stimulate uterine contractions in labor.

See Oxytocin.

#### PITRESSIN

An aq. soln. containing the pressor and diuretic-antidiuretic principle of the pituitary gland, posterior lobe; raises blood pressure, promotes muscular tone; used in post-operative ileus, shock, enuresis, diabetes insipidus.

See Vasopressin.

#### PITTARELLI REACTION FOR CREATININE AND UREA

5 cc. of the strongly alkaline test solution are treated with 0.05 gm. sodium nitroprusside and 0.1 gm. potassium persulfate. A red color develops within 20-30 seconds, sensitivity for creatinine—1:500-00; for uric acid 1:500.

Reference: Arch. farmacol. sper. 45, 173 (1928).

#### PITTARELLI TEST FOR ASCORBIC ACID (VITAMIN C)

I. A mixture of the vitamin solution is slowly treated with dilute ammonium thiocyanate forming a white precipitate turning to a green color on further addition of ammonium thiocyanate.

II. Mercurous chloride is precipitated from mercuric chloride solution by the vitamin.

Reference: Biochim. terap. sper. 22, 100 (1936).

#### PITUITARY, ANTI-INSULIN EFFECT OF

See Carbohydrate Metabolism.

#### PITUITRIN

Aqueous extract of the posterior lobe of the pituitary. See Oxytocin.

pK

A convenient method of expres-

sing and plotting ionization constants. It is defined as the negative logarithm of the ionization constant.

#### PLACENTA

Common interlocking tissue organ of mother and foetus in mammals, serving for passage of nutrients and wastes; the after-birth.

#### PLANE POLARIZED LIGHT

Light vibrating in one plane along the path of propagation. It is usually obtained by passing ordinary light through polarizing crystals.

#### PLANKTON

Open sea fauna and flora of microscopic size.

#### PLANOCAINE

See Procaine.

#### PLANTS, DEPENDENT

See Digestion.

#### PLANT GROWTH

See Growth.

#### PLANT GROWTH HORMONES

The term hormone means a chemical messenger, i.e., a substance which is produced in one part of the organism and is then transported to other parts where it exerts its effect. It is restricted further to substances active in minute amounts. The substances controlling growth in plants are of many types: water, the nutrient salts (K, Ca, Mg, Fe, Mn, Zn, Cu, Mo, NO<sub>3</sub>, PO<sub>4</sub>, SO<sub>4</sub>, BO<sub>3</sub>), carbohydrates, amino acids, and purines all influence growth. These are not hormones, however. The most important growth hormones are the auxins, a group of ether-soluble, unsaturated organic acids whose structure is discussed below.

### Assay Methods

The auxins were discovered through the experiment of Páal in 1918 in which the tip of the oat coleoptile was cut off and then replaced asymmetrically, i.e., to one side (Fig. 1). The side below the replaced tip grew more than the opposite side, causing curvature. Went then showed that a similar result was obtained if the tips were placed first on agar and the agar then applied to one side of decapitated coleoptiles. The curvature so obtained is proportional to the concentration of the hormone in the agar, up to a limiting maximum angle (Fig. 2). Skoog has increased the sensitivity of the test some five or six times by removing the seed 24 hours beforehand.

If the agar be placed symmetrically on top of the coleoptile, the increased straight growth is also proportional to concentration of hormone, and this straight growth could be used for assay. Other methods of assay have been developed. If stems of etiolated pea plants (Went), flower stalks of dandelion (Jost), or coleoptiles of oat or maize are slit lengthwise and immersed in a solution of the hormone the two halves curve inwards, while in water alone they curve outwards. A modification of this test (Thimann and Schneider) gives measurable response to 0.003 mg. active substance per liter of solution.

The essence of the assay methods is, of course, to deprive the test plant as far as possible of its own auxin supply, just as animals on vitamin-deficient diets are used for vitamin assay. Since auxins are produced in light, etiolated plants are desirable, the buds, tips, or other producing zones being removed. However, some workers use

green plants in the light but the procedure is obviously open to objection, though usable results have been so obtained.

### Chemistry

Auxins are produced in the coleoptile tip, in growing buds, embryos, and young leaves of all plants studied, and to some extent in all green tissue in the light. They are also formed by many fungi and bacteria. On account of their presence in plant material, auxins are found in blood, animal tissues, and in considerable amounts in urine. From urine and from corn germ oil Kögl, Haagen Smit and Erxleben isolated auxentriolic acid (auxin a) and auxenolonic acid (auxin b); from urine was also isolated indole-3-acetic acid. Indole-3-acetic acid was isolated from yeast by Kögl and Kostermans, from the fungus *Rhizopus suinus* by Thimann, and recently from corn meal by Haagen-Smit, Leech, and Bergren. A large number of synthetic substances are active as auxins. These all comprise an unsaturated or an aromatic ring, with an acid sidechain having at least one methylene group between the ring and the carboxyl (Fig. 3). Salts of the acids are active, but there is some reason to believe that at the pH of plant sap (about 6.0) it is the undissociated acid that is active. Application of inorganic acid to a cut surface (the cut allows entry) will often accelerate growth, probably by formation of the free auxin acid from its salts. Esters and amides are also active, though not in all cases; whether they are converted to the free acid in the plant is not certain. Activity varies in an alternating manner with length of side chain; it varies widely with the nature of the ring, indole, indene, and naph-



thalene giving much more activity than benzene, cyclohexene, pyrrole, or cyclopentene rings; it is affected by substitution in the ring and is destroyed by the saturation of the ring (Fig. 4); with unsaturated side chains (as far as studied) the *cis*-form is active, the *trans*- (Fig. 5) not. From a consideration of all recorded active substances, Koepfli, Thimann and Went concluded that "the specificity of physiological activity does not necessarily depend on the nucleus of a substance but upon a particular molecular configuration. The minimum structural requirements for cell elongation activity in higher plants . . . are (a) a ring system as nucleus, (b) a double bond in this ring, (c) a side chain, (d) a carboxyl group (or a structure readily converted to a carboxyl) on this side chain at least one carbon atom removed from the ring, and (e) a particular space relationship between the ring and the carboxyl group. Recently Zimmerman and Hitchcock have found an apparent exception, activity (on green plants in the light) being exerted by 2-bromo-3-nitro benzoic acid, in which the COOH group is not separated from the ring. At the time of writing, this has not been tested under critical conditions.

### Tropisms

Shoots curve toward a source of light and away from gravity. These curvatures are due to unequal auxin distribution, the lower side in the case of the geotropism, or the shaded side in phototropism, receiving more auxin than the opposite side. The mechanism of perception is not understood; in the case of light the spectral distribution of response corresponds to that of the carotenoids present and the extreme sensitivity of the tip of the coleop-

tile, as compared with the base, agrees with the presence of carotenoids almost wholly in the tip (Bünning). The connection between perception by the carotenoids and the effect on transport of auxin is unknown. The action of light is complicated by two further factors: inactivation of some of the auxin by light, and reduction in the responsiveness of the tissue in presence of light. It is the latter which is largely responsible for the fact that green plants in light do not elongate as much as in the dark.

### Root Formation

Evidence that formation of roots on stems or cuttings is controlled by a hormone was first given by Bouillenne and Went in Java; they ascribed the action to a special substance, rhizocaline. In attempts to purify this, Thimann and Went found that the activity of various preparations during purification went parallel with the auxin activity. Finally it was proven (Thimann and Koepfli) that pure indole-3-acetic acid causes root formation in the standard test on etiolated pea cuttings, and Kögl found the same thing with *Tradescantia* internodes. It is now clear that virtually all auxins cause root formation. The most active are indole-3-acetic and indole-3-butyric acids and naphthalene-1-acetic acid and its amide. These are marketed in alcoholic solution, or dissolved in lanoline, or as powders mixed with talc under various trade names. They are usually applied to the base of the cutting in concentrations (aqueous solution) of from 25 to 200 mg. per liter, according to the sensitivity of the plant material, for 24 hours. In talc or lanoline the concentrations are from 10 to 100 times as high. The cuttings are then kept in



the propagation bench for periods between 10 days and 4 months. Auxins accelerate rooting, increase the number of roots per cutting, and cause cuttings to root which would not do so otherwise. Certain plants, however, including many forest trees, resist even optimal auxin treatment. Seeds may also be treated before planting, to obtain increased root systems, with a subsequent corresponding increase in growth rate, plant size, or even fruit set.

#### Inhibition of Growth

Although root formation is induced by auxins, the elongation of roots is inhibited. Extremely low concentrations, however, (about  $10^{-9}$  molal) somewhat accelerate root growth. The significance of this for normal growth is unknown since the root tip produces only moderate amounts of auxin.

The inhibition of lateral buds by auxins is of great importance. The terminal bud on a shoot inhibits development of laterals, and when it is removed the laterals develop. This is the basis of pruning. The inhibition was shown by Thimann and Skoog to be due to the auxin formed by the terminal bud, and it can be imitated by supplying a pure auxin to the cut surface after pruning. A few of the known auxins, particularly phenylacetic acid, will not cause this inhibition, but most do. Dormant buds do not produce appreciable amounts of auxin, and consequently do not inhibit other buds. In dwarf plants the auxin formed in the terminal bud is destroyed more rapidly than normal (van Overbeek); this accounts not only for the reduced growth but also for the greater branching or bushiness which commonly accompanies

dwarfing, because insufficient auxin is produced to keep the lateral buds inhibited.

Allied to bud inhibition is the inhibition of the abscission layer. Mature leaves and fruits fall from the plant due to formation of a special layer of cells whose walls pull apart from one another and thus virtually sever the organ from the stem. In some way this is inhibited by auxins. The phenomenon has found important application by apple orchardists, who use an auxin spray (usually naphthalene-1-acetic acid) towards the end of the season to prevent early fruit drop.

#### Other Functions of Auxins

Auxins are present in algae, and it is probable that they control growth in them as in higher plants. Although widely formed by fungi and bacteria, their role in the growth of these organisms is uncertain.

The activation of cambium in trees in the spring, leading to rapid cell division and the laying down of xylem and phloem, is apparently under the control of auxin. The developing young buds produce considerable amounts of auxin (see above) and this is transported downwards into the cambium below them. The transit of the auxin down the stem roughly parallels the downward spread of cambial activity. Snow, Söding and others have shown that introduction of indole-acetic acid into the stem will cause great activity of the cambium, many layers of wood being laid down. With such artificial auxin, however, the effect does not spread so far downwards as when caused by buds.

The growth of the ovary, after fertilization, into a fruit, is started,

apparently, by the auxin present in pollen. By removing the anthers and, instead, applying auxin in lanolin, or as spray, directly to the ovary, Gustafson and other workers have caused fruit to develop without seed (parthenocarpy). Seedless fruits of tomato, squash, pear, holly, and many other plants have been so produced.

High concentrations of auxins applied locally to young stems cause swellings, tumors, etc. Some of the phenomena accompanying bacterial and other infections in plants (e.g., crown gall, root nodules, etc.) are believed to be due to the local liberation of large amounts of auxins. In nodules it is clear that large quantities of free auxin are formed. There is good evidence that a large reservoir of auxin in an inactive bound form is present in most plant tissues, and this may be the source from which the invading organism produces free auxin. The auxin may also, however, consist of indole-acetic acid produced by oxidative deamination of tryptophane, which is, of course, present in plant proteins.

#### Transport and Mode of Action

The outstanding peculiarity of the auxins is that in the plant they are produced always at apical or terminal points, and are transported thence towards the base. This transport is strictly polar, i.e., it moves only from apex toward base, even in cut, isolated sections. The polar transport is not influenced by inverting the section, in other words the auxin continues to move from the morphologically apical to the morphologically basal end. However, turning the section through 90° causes partial diversion of auxin to one side (cf. geotropism above).

Also, as was shown strikingly by van der Weij, auxin will continue to be transported polarly even against an externally applied gradient of auxin concentration. If applied to the roots, or to the base of cuttings, auxins are drawn up in the transpiration stream just as are salts and other solutes, but as soon as they diffuse out of the xylem into living tissue they are re-exported polarly downward.

A supply of carbohydrate is needed for auxin to cause growth. In part this is required for cell-wall formation, since the wall consists of cellulose, which is built of hexose units. In part, however, it is required for respiration. Growth goes on only in  $O_2$  and is poisoned by HCN and by  $ICH_2COOH$  just as is respiration. There is good evidence that the growth process is linked to one part of the total respiration, a part which involves also malic or fumaric acid. The inhibition of growth by  $ICH_2COOH$  is removed by adding malate. Starved coleoptiles show little response to auxin unless malate is added as well. The combination of auxin and malate then causes an increase in respiration which closely parallels the increase in growth. It has also been shown by Sweeney and Thimann that application of auxin to cut coleoptiles causes an immediate increase in the rate of protoplasmic streaming in the cells. This increased rate requires carbohydrate for its maintenance, is prevented by iodoacetate, and promoted by malate. It requires oxygen. There is thus a very close parallel between the action of auxin on growth, respiration, and streaming. The small part of the respiration involved represents less than 10 per cent of the total  $O_2$  consumption

of the tissue, but apparently controls all of the growth. Whether these deductions hold true for other tissues than the coleoptile remains to be proven.

### Other Growth Hormones

For the growth of isolated roots in culture solution thiamin is essential. Some roots also require nicotinic acid or pyridoxin (Bonner). Since these materials are formed in the leaves and transported to the roots, they must be considered plant hormones. In the rooting of cuttings, auxin causes initiation of roots, but a few species need application of thiamin for the roots to grow out. Biotin and adenine also contribute to root formation in some instances. If plants produce unusually small amounts of thiamin, their growth may be accelerated by supplying thiamin to the whole plant by watering with a dilute solution (about 0.5 mg. per liter). This is true for camellias but for most other plants has been disputed and conflicting results have been obtained.

The growth of isolated embryos in culture provides an excellent test for the necessity of growth substances. They require in addition to thiamin both biotin and pantothenic acid. Growth is in some cases also stimulated by estrogens. If very young, still another factor, as yet unidentified but present in coconut milk, has been shown to be essential by van Overbeek, Conklin, and Blakeslee. Coconut milk is essentially a liquid endosperm; this factor is normally supplied to the embryo by the endosperm. Apparently it is needed only for the earliest stages of development.

When tissues are injured, the cells near the wound elongate or divide. This effect is due to a

"wound hormone" set free by the injury. Extracts of ground or wounded tissues are active in causing this reaction, and the cells of the inner pericarp of the bean pod, which are especially responsive, have been used as assay material. When a drop of the active solution is placed on this tissue, a small wart or nodule is formed, the height of which is linearly proportional, within limits, to the concentration of the active substance. This wound tissue may involve cell division or it may not, according to the variety of bean employed. In this way English and Bonner isolated traumatic acid, or 1-decane-1-10-dicarboxylic acid, which is responsible for at least a large part of the wound hormone effect. There are also small nonspecific effects, exerted by water, neutral salts, auxins, and citric acid, but these never approach the magnitude of the traumatic acid response. The saturated acids, decane-1-10 dicarboxylic and sebacic ( $C_{10}H_{18}O_4$ ) possess about half the activity of traumatic acid.

When leaves of *Mimosa pudica*, the "sensitive plant," are touched, burned, or otherwise stimulated, a stimulus travels down the petiole causing the leaflets to fold and the petiole to droop. Other leaves above or below may be stimulated. There is good evidence that this stimulus is due to a rapidly transported substance of hormonal nature. A hy- and certain anthraquinone glucodroxyacid of unknown constitution, sides, have been implicated.

In order to account for the growth of leaf blades and other organs, Went has postulated the existence of a number of organ-forming substances, phyllocaline controlling leaf growth, caulocaline

controlling stem growth, and rhizocaline controlling root growth. These are considered to act in addition to auxin. The evidence for them is as yet indirect and not entirely conclusive.

The phenomena of flower formation, particularly the influence of the photo-period on flowering, has given rise to the concept of a flowering hormone or florigen. There is indeed evidence that such a substance is produced in leaves and transported to the buds, causing therein the change from the vegetative to the flowering condition, but there is no clear proof of its hormonal nature.

#### LITERATURE

- Phytohormones, F. W. Went and K. V. Thimann, New York, Macmillan, 1937.
- Growth Hormones in Plants, P. Boysen Jensen, transl., G. Avery and P. Burkholder, New York, McGraw-Hill, 1936.
- Plant Growth Hormones, K. V. Thimann and J. Bonner, *Physiol. Reviews*, Vol. 18, No. 4, pp. 524-553, 1938.
- Auxins and the Inhibition of Plant Growth, K. V. Thimann, *Biol. Reviews*, Vol. 14, pp. 314-337, 1939.
- Plant-growth Regulators, J. W. Mitchell and R. R. Rice, U. S. Department of Agriculture, Misc. Publ. No. 495.
- Die Wuchsstoffe der Pflanzen, G. Schlenker and C. Rosenthal, Munich, J. F. Lehmann, 1937.
- Auxin, the plant growth-hormone, F. W. Went, *Bot. Rev.*, Vol. 1, pp. 163-182, 1935.
- The hormones and vitamins of plant growth, J. Bonner, *Scientific Monthly*, Vol. 47, pp. 439-448, 1938.
- Plant tissue cultures, P. R. White, *Ann. Rev. Biochem.*, Vol. 11, pp. 615-628, 1942.
- Further experiments with growth substances and the rooting of cuttings,

M. A. H. Tincker, *J. Roy. Hort. Soc.*, Vol. 63, pp. 210-230, 1938.

See also articles on Growth Hormones of Higher Plants in *Ann. Rev. Biochem.*, 1935 (K. V. Thimann), 1938 (P. Boysen Jensen), 1939 (F. W. Went).

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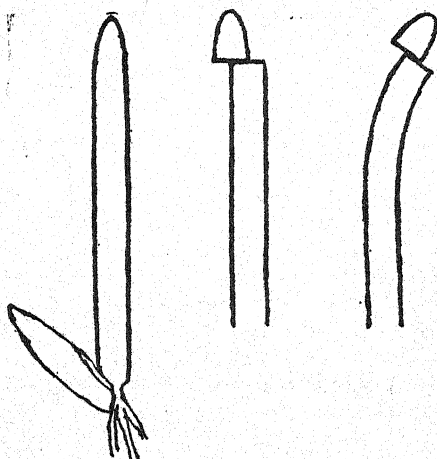
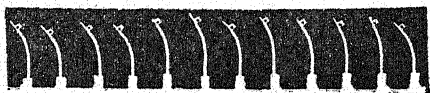
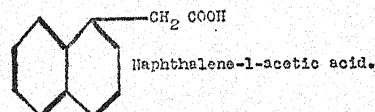
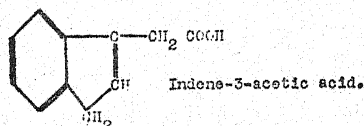
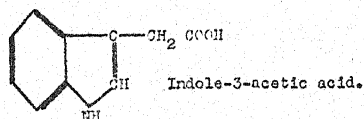
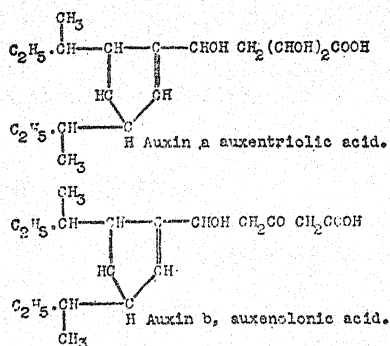


Fig. 1. The experiment of Paal. Left, intact oat seedling; center, tip removed and replaced to one side; right, curvature resulting. The experiment was carried out first with Coix seedlings. (From K. V. Thimann, *J. Franklin Inst.*, 229: 337-346, 1940).

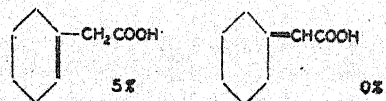
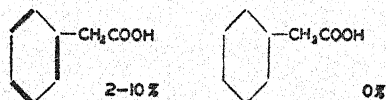
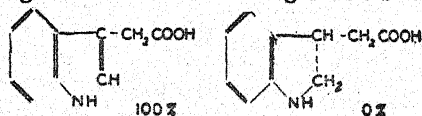
Fig. 2. Oat seedlings with tips removed



and blocks of agar containing growth hormone applied. Photographed 100 minutes later. First carried out by Went, 1927. (From K. V. Thimann, *J. Franklin Inst.*, 229: 337-346, 1940).



**Fig. 4. Influence of the ring double bond**

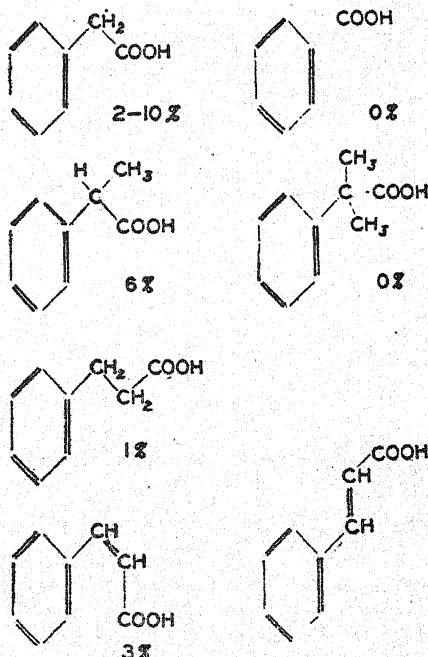


on auxin activity.

### Activities expressed

as % of that of indole-acetic acid. Slit pea stem test. (From K. V. Thimann, Plant Physiol., 13: 437-449, 1938).

Fig. 5. Influence of spatial relations of



the molecule on auxin activity. Activities and test method as in figure 4. (From K. V. Thimann, *Plant Physiol.*, 13: 437-449, 1938).

## PLANTS, INDEPENDENT

**See Digestion.**

## PLAOUE COUNT

See Bacteriophage.

## PLASMA

Blood serum from which the fibrinogen has not been removed.

## PLASMALOGENS

Acetal phospholipides which are present in small quantities in tissues and contain palmitaldehyde and stearaldehyde in place of fatty acids.



**PLASMA MEMBRANE**

Cell membrane.

**PLASMAPHORESIS**

The reduction of serum protein to a very low level by bleeding, removal of the cells from the exuded blood and reinjection of the cells in a protein-free solution.

**PLASMOCHIN**

N-diethylamino-isopentyl-8-amino-6-methoxyquinoline, light yellow; used in malaria to destroy gametes of parasite.

**PLASMODIUM**

See Protoplasm.

**PLASMOLYSIS**

The exosmosis of water from a cell, as when the cell is placed in a hypertonic solution. In a plasmolyzed cell the protoplasm shrinks away from the cell wall. See Permeability, Protoplasm.

**PLASMOLYTIC METHOD**

A method of determining the osmotic pressure of cells by placing the cell in solutions of varying concentrations. By microscopically observing the resulting turgidity or plasmolysis of the cell one can determine the concentration of a solution which is isotonic to the cell and from this its osmotic pressure.

**PLASTEINS**

The name given to the group of proteins synthesized in the presence of pepsin.

**PLASTID**

Unnucleated, chlorophyllic cell.

**PLASTICITY**

The resistance that a solid or semi-solid offers to deformation of shape by shear or flow. In many respects analogous to viscosity in a liquid.

**PLATELETS**

Cellular constituents of blood, ordinarily numbering between 250,000-400,000/ccm. They contain the cephalin, etc., which is necessary to blood clotting.

**PLATYHELMINTHES**

Class of flat worms and numerous parasitic worms.

**PLECTRIDIDIUM**

**CELLULOLYTICUM**

See Cellulose Decomposition.

**PLEURA**

See Respiration.

**PLUMMER-MENDENHALL**

**REACTION FOR**

**THEOPHYLLINE**

A mixture of equal volumes of methyl alcohol solutions of saturated cupric acetate and theophylline gives a pale blue-green precipitate. Sensitivity—0.2 mg. per cc.

Reference: J. Pharmacol. 60, 116 (1937).

**PNEUMOCOCCUS**

See Microbiology.

**PNEUMONIA**

Inflammation of the lungs due to infection by bacteria or specific viruses after a period of incubation followed by chills and fever, pain in chest and many systemic symptoms. The sputum is typed for the different kinds of pneumococci, and so is the blood, and even lung sections may be taken. Complications involve pleurisy, pericarditis and pulmonary edema. Serum therapy in order of frequency employs antisera of types I, II, V, VIII, VII, IV and XIV. Sulfapyridine therapy is used for all types. In emergency the sodium salt of sulfapyridine is injected intravenously. The caution in the



use of sulfa drugs is to watch out for the development of acute hemolytic anemia and anemia, agranulocytosis. Oxygen therapy to prevent cyanosis is frequently indicated especially in the case of children and infants. Sulfathiazole has also been used with success.

**PODAGRA**

See Gout.

**PODOXYHYLLIN**

A mixture of resins of the American mandrake; a purgative and liver stimulant.

**pOH**

A term, analogous to pH, sometimes used to express directly the degree of alkalinity of a solution.

**POIKILOTHERMIC**

Cold blooded.

**POISE**

The unit of viscosity. It is the force (one dyne) which, when exerted on a unit area between two parallel planes one square cm. in area and one cm. apart, produces a difference in streaming between the two planes of one cm. velocity per second.

**POISEUILLE'S LAW**

See Protoplasm.

**POISONING,  
ACUTE AND CHRONIC**

See Toxicology.

**POISONING, CUMULATIVE**

See Toxicology.

**POISONING, METALLIC**

See Toxicology.

**POISONS**

See Toxicology.

**POISON IVY**

Rhus toxicodendron; poison vine; poison oak; contains toxicoden-

drol, toxicodendric acid and a resin; has been used as a rubefacient and irritant and internally in rheumatism.

**POLARIMETER**

An instrument used to measure the number of degrees an optically active substance rotates the plane of polarized light. It consists of two prisms so arranged that polarized light from the first prism can pass through the second when the instrument is set at zero. The rotation of a substance is determined by placing it between the two prisms and rotating the second to compensate for the change that the substance has caused in the plane of the light emerging from the first.

**POLARIZED LIGHT.**

See Plane Polarized Light.

**POLENSKE NUMBER**

The number of cc. of 0.1N KOH needed to neutralize the non-volatile acids obtained by the saponification of 5 grams of fat or oil.

**POLIOMYELITIS**

Infantile spinal paralysis; Heine-Medin disease; an acute infectious disease caused by a filtrable virus after an incubation period and showing involvement of the central nervous system in a meningitis stage and in an acute paralytic stage of many varieties, followed by atrophies in a prolonged post-inflammatory stage. The chief mainstay in its treatment is convalescents' serum.

**POLLINOSIS**

See Hay Fever.

**POLYASES**

Carbohydrases that hydrolyze polysaccharides.

**POLYDISPERSION**

See Sol, Polydisperse.

**POLYGALITOL**

1:5-anhydromannitol, found in *Polygala* species; sweet, m.p. 142°.

**POLYMENORRHEA**

Metrorrhagia (old term); too frequent menstrual flow.

**POLYNUCLEOTIDASE**

A heat resistant enzyme which becomes inactive at 85-95° but regains its activity on cooling to 60° (Dubos).

**POLYPEPTIDASES**

Peptidases which split peptides more complex than two amino acid groups, distinguished as amino polypeptidases and carboxy-polypeptidases.

**POLYPEPTIDES**

The combination of two or more amino acids, the amino group of one molecule combining with the carboxyl group of the other amino acid, with a molecule of water being split off in the process.

**POLYPEPTIDE TESTS**

See Abderhalden-Schmidt.

**POLYPHENOL OXIDASE**

(1) Potato—a copper protein enzyme which catalyzes the oxidation of polyphenols (catechol, adrenaline, dihydroxyphenylalanine) to quinones; can absorb CO.  
(2) *Agaricus Campestris* — of mushroom origin, qualitatively as above.

**POLYPHENOLS, TESTS FOR**

See Bezssonov.

**POLYPS**

See Gastro-Enterology.

**POLYSACCHARIDASES**

Also see Enzymes, Non-Proteolytic.

**POLYSACCHARIDES**

Carbohydrates formed by the condensation of two or more monosaccharides. Usually refers to the condensation product of an indefinite but very large number of monosaccharides, such as in starch and cellulose. They generally form hydrophilic colloids rather than true solutions.

**POLYSACCHARIDES, CLASSIFICATION OF**

A convenient classification (Gortner) is:

- I. Starches or Hexosans  
Glucosans, fructosans, mannosans, galactosans, amyloids.
- II. Gums or Mucilages  
Pentosans, natural gums, pectins, plant mucilages.
- III. Polymerized Glucosamine  
Chitin.
- IV. Celluloses  
Hemicelluloses, true celluloses, compound celluloses.

One must remember that non-carbohydrate groups are frequently also present in the natural compounds.

For details see individual entries. See also Carbohydrates, Classification of.

**POLYZIME**

A preparation of the enzymes of *Aspergillus oryzae*.

**PONS REAGENT FOR ALBUMIN**

A 1:1000 aqueous solution of the sodium salt of sulfochondroitin acid is a specific reagent for albumin, forming precipitates in dilute acetic acid solutions. Limit of detection—5 mg. albumin per liter. Reference: Rev. Pharm. Flanders 1910, 73.

**POPULIN**

$C_{20}H_{22}O_8$ ; 6-benzoylsalicin; a glycoside of the bark of *Populus*, consisting of glucose, saligenin and benzoic acid; needles, m.p.  $180^\circ$ ; used as antipyretic in urinary affections.

**PORIFERA**

Class of sponges.

**PORPHYRINE TESTS,  
IN URINE**

See Brugsch.

**PORPHYRINS**

A group of pigments, part of the hemoglobins and chlorophyll, possessing the porphyrin structure. The more important porphyrins derived from hematin are:

Hemin —  $C_{34}H_{32}O_4N_4FeCl$

Protoporphyrin —  $C_{34}H_{34}O_4N_4$

Hematoporphyrin —  $C_{34}H_{38}O_6N_4$

Mesoporphyrin —  $C_{34}H_{38}O_4N_4$

Aetioporphyrin —  $C_{32}H_{38}N_4$

Deuteroporphyrin —  $C_{30}H_{30}O_4N_4$

Deuterohemin —  $C_{30}H_{28}O_4N_4FeCl$   
which differ in the nature of the side chains which are methyl, ethyl,  $-CH_2CH_2COOH$  and  $CH_2CH_3$ .

**PORPHYROPSIN**

A compound of the retinae of fresh water fishes, analogous to rhodopsin, consisting of a retinene component and vitamin  $A_2$ .

**PORPHYROXINE**

$C_{19}H_{23}O_4N$ ; prisms, m.p.  $134-135^\circ$ ; opium; an alkaloid of opium. The hydrochloride crystallizes as prismatic needles, m.p.  $155^\circ$ .

**POSITIVE ADSORPTION**

See Adsorption.

**POSITIVE NITROGEN  
BALANCE**

See Nitrogen Balance.

**POST ABSORPTIVE  
CONDITION**

State of an animal in which last food intake does not essentially affect its metabolic rate. (Twelve hours after last food for humans, dogs and rats, four days for ruminants.) M. K.

**POST-ABSORPTIVE  
METABOLISM**

See Basal Metabolism.

**POSTURAL ALBUMINURIA**

See Orthostatic Albuminuria.

**POSTURAL COORDINATION**

See Neurophysiology.

**POTASSIUM ION**

See Bioelectric Potentials.

**POTASSIUM TEST**

See Fredholm.

**POTENTIALS, BIOELECTRIC**

It is a century since the work of Du Bois Reymond clearly demonstrated the existence of potentials in tissues and changes in these potentials with physiological state. Although the energy involved in bioelectric phenomena is negligible, they contribute the most important mechanisms for the release and control of action. For, probably, all living cells have voltages across their outer membrane (of the order of 50 mV); these voltages and the membrane resistance (some hundreds of ohms per square centimeter) across which they act drop sharply during excitation and response; and the resulting currents flow to other cells and cell regions and so help to pass on activity. Such bioelectric changes are, indeed, at the basis of the propagated nerve impulse, itself.

The very elongated cells or fibres of nerve and striated muscle and the large cells of certain algae

(*Nitella*, *Valonia*, *Halicystis*, *Chara*) have especially lent themselves to the analysis of bioelectric phenomena; but potential, resistance and capacity measurements on the heart, skin, eye, gut, glands, brain, plant structures, etc., have been of great use as a means of studying these organs and tissues. The very special electric organs evolved by certain rays, skates, eels, etc., as a weapon of attack or defense and able to deliver shocks at several hundred volts—have also been useful objects for study, since they are only modified muscle elements built in series instead of in parallel.

When a microelectrode is thrust into a single cell or fibre, it registers about 50 mV negative to a similar electrode placed outside the unit. With both outside or both inside, essentially no potential is recorded when the system is at rest—indicating that the potential is generated across the membrane. (Some potentials exist from pole to pole of intact elongated cells, but these are as yet little studied.) The membrane potential is maintained, despite leakage of current, by the cell metabolism. When cell oxidations are stopped by deprivation of oxygen or by respiration poisons (cyanide, anaesthetics; or by blocking fermentation) the potential falls. The cell thus acts as a self-charging storage battery.

The exact mechanism for transforming chemical into electrical energy is not known, but the potassium ion is probably involved. Cells regularly contain potassium salts in their protoplasm (or inner sap) in many times higher concentration than these salts are present in surrounding fluids; and the membrane potential is about what it should be for such concentration differen-

ces. Further, when metabolism is interfered with the internal potassium leaks out; also, when outside potassium is raised the membrane potential falls. Other ions may well play a role, and other substances, especially acetylcholine, are also able to influence strongly the membrane potential.

In nerve or muscle, with units several centimeters long arranged parallel to each other, it is possible to follow electric phenomena on the gross structure. A narrow flat muscle (the frog's *sartorius*) has been much used. When ordinary electrodes are placed on the two ends of an isolated but essentially uninjured specimen they record little or no potential. When one end is cut off, or the fibres there otherwise injured, that electrode becomes negative (some 15 mV) to the other. This injury or resting potential (or current, as the case may be) is really a portion of the membrane potential, the injured region being in effect a partial lead from the inside. If, now, the muscle is made to contract the potential difference becomes momentarily less. Since the injured end does not change, this means that the electrode outside the intact portion of the muscle fibres has become temporarily less positive. This is the action potential (or current)—a decrease of the voltage across the cell membrane when the cell is active. It can be demonstrated with a pair of microelectrodes across the membrane, as in the case of the resting membrane potential; and, indeed, the change during activity may be so great that the resting potential is actually reversed in direction.

The action potential is not simultaneously present over an entire nerve or muscle fibre but travels

from the region of stimulation. In human nerves, the nerve impulse and the attendant action potential travel at rates up to 150 meters a second; in muscle, propagation is under 5 meters a second. In either case, the change spreads away from the point stimulated, equally well in either direction. If, therefore, one end of the muscle is stimulated and electrodes are placed at two positions along the muscle's length, the action potential will reach the near one first, and make it negative to the far one, while shortly after the far one will become active and negative to the near one. Such a diphasic response is obtained from intact tissue. If the far end has been previously injured so that it cannot become active, then only the first negative wave occurs and the response is monophasic. A monophasic action potential can also be obtained with microelectrodes across a single portion of the membrane.

Besides the simple resting and action potentials, other pre- and after-potentials are related to excitation and response, especially in nerve. The latter may be positive and negative alternately and may last many seconds or even minutes beyond the main action potential, or spike, which is ordinarily complete within a thousandth of a second. They, however, rarely amount to more than a few per cent of the spike in voltage. The prepotentials are associated with excitation and occur before the spike or, when stimuli are too weak to evoke a full response, without it. They may also oscillate, as do the after-potentials, but more rapidly.

Membrane potential and resistance are profoundly related to the spread of the nerve or muscle (or

heart, etc.) impulse. The region initially stimulated loses its polarization, the potential across its membrane; and this loss of polarization leads to the cell response. Thus the negative pole of a current, applied to the outside of a muscle, neutralizes the original membrane potential (which is positive outside), and the positive current pole increases it. The cell is depolarized at the negative pole and it is here, not at the positive pole or anywhere between, that the response begins. As a region of membrane is depolarized some critical physicochemical reaction occurs in the membrane—the full action potential develops and the membrane's electrical resistance falls greatly. This causes currents to flow between the active part of the membrane and adjacent regions which are still at rest. But these currents depolarize, and so stimulate, these new regions which, in turn, give their explosive action and cause currents to flow through yet further resting regions. This propagated excitation of each resting region by the oncoming activity is the mechanism of transmission in the body—of the nerve and muscle impulse.

Whether electric currents are similarly responsible for excitation from one cell to another is not so certainly established. Receptors (see section on the nervous system) do develop potentials when stimulated which might excite the sensory nerve fibers. Currents do flow across nerve cells and fibers at synapses, and between nerve fibers and muscle (with the aid of special connecting end-plates and their potentials), and might easily excite across the cell junctions. It is also possible, however, that acetylcholine and other substances, which



are freed in connection with the activity of nerves and their endings and which can excite effectors and depolarize them, are involved. Probably electrical and chemical mechanisms cooperate in transmission across junctions as they do in transmission along nerve or muscle fibers.

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**POTENTIALS, BIOLOGICAL**  
See Potentials, Bioelectric.

**POTENTIALS, DIFFUSION**  
See Diffusion Potential.

**POTENTIALS, MEMBRANE**  
See Protoplasm.

**POTENTIOMETRIC  
TITRATION**

A titration whose course is followed by measuring the changes in the e.m.f., due to changes in pH, which occur when one reagent is added to the other.

**POZZI-ESCOT MICRO-TEST  
FOR AMINO BENZOIC ACID**

The ester-containing urine distillate is saponified in a closed tube with sodium hydroxide solution, neutralized and treated with copper sulfate solution. Blue crystals of copper anthranilate are formed if o-aminobenzoic acid is present. Reference: Rev. cienc. (Peru) 38, 67 (1936).

**POZZI-ESCOT REACTION FOR  
ROTENONE**

When sulfuric acid solutions of mercuric oxide and rotenone are mixed, a white precipitate insoluble in the cold is formed. The precipitate dissolves on heating, yielding an intensely colored solution.

Reference: Rev. cienc. facultad cienc. biol. fis. mat. univ. major de San Marcos (Peru) 38, 21 (1936).

**P. P. FACTOR**

See Pellagra-Preventive Factor.

**PREBULA-McCOLLUM  
REACTION FOR VITAMIN B<sub>1</sub>**

Vitamin B<sub>1</sub> gives a characteristic purple-red compound with a diazotized solution of either p-aminoacetanilid or methyl-p-aminophenylketone. The compound is stable, very insoluble in water and completely soluble in xylene.

Reference: Science 84, 488 (1936).

**PRECIPITIN**

See Immunological Phenomena.

**PRECIPITINOGEN**

See Immunological Phenomena.

**PREGNANCY TESTS**

See Abderhalden-Schmidt, Kaminitzer-Joseph, Kappeler-Adler.

**PREGNANDIOL**

C<sub>21</sub>H<sub>36</sub>O<sub>2</sub>; m.p. 235°; an inactive sterol found with progesterone in the corpus luteum and in pregnancy urine. Its structure is that of a saturated progesterone with the two carbonyl groups reduced to alcoholic groups.

**PRE-POTENTIALS**

See Potentials, Bioelectric.

**PRESSURE, OSMOTIC**

See Protoplasm.

**PRIMEVERIN**

See Primeverose.

**PRIMEVEROSE**

Glucose-6-beta-d-xyloside, a constituent of the glycosides, primeverin, gaultherin, rhamnucosin, genticaulin; m.p. 208°.

**PROCAINE**

Planocaine; novocaine; ethocaine; diethylamino-ethyl-p-aminobenzoate; m.p. 59-61°; used as hydrochloride for local anaesthesia; less toxic than cocaine.



**PROCAINE TEST**

See Riegel-William.

**PRO- $\gamma$ -CAROTENE**

A precursor of  $\gamma$ -carotene,  $C_{40}H_{56}$ .

**PRODIGIOSIN**

A bacterial pigment.

**PROGESTERONE**

$C_{21}H_{30}O_2$ ; needles, m.p.  $121^\circ$ , prisms m.p.  $128^\circ$ ; hormone of the corpus luteum. It inhibits the release of ova during pregnancy, and is apparently necessary for the maintainance of the pregnancy. Given subcutaneously in oil solution. One gram=1000 International Units.

**PROGESTIN..**

See Progesterone.

**PROGYNON**

A trade name for the female sex hormone.

**PROLACTIN**

Galactin; mammotropin. The protein hormone of the anterior pituitary that stimulates the mammary glands to secretion.

**PROLACTIN UNITS**

The assay of the activity of a preparation in increasing the weight of the crop sac of the pigeon dove in terms of 0.1 gram of an International standard preparation.

**PROLAMINES**

See Gliadins.

**PROLAN A**

See Follicle Stimulating Hormone.

**PROLAN B**

See Luteinizing Hormone.

**PROLIDASE**

A proteolytic enzyme that hydrolyzes peptide linkages involving the imino group of proline.

**PROLINASE**

The only proteolytic enzyme that splits a peptide linkage where the carboxy group of proline is involved.

**PROLINBETAINE**

See Stachydrine.

**1-PROLINE**

Pyrrolidine-2-carboxylic acid;  $C_5H_9O_2N$ ; m.p.  $220-2^\circ C$ ; an amino acid found in casein, gelatin and cereal proteins.

**PROLINE METABOLISM**

Proline is oxidized to glutamic acid, which then may be further oxidized to ammonia and ketoglutaric acid, which on  $\beta$ -oxidation ultimately yields  $CO_2$  and  $H_2O$ . Alternately, the glutamic acid may combine with ammonia to yield glutamine. It is anti-ketogenic as it can form glucose.

**PROLYCOPENE**

A naturally occurring stereoisomer of lycopene, especially in the "tangerine tomato." It is a  $C_{40}$  carotenoid and is one of 72 possible isomers of lycopene.

Reference: L. Zechmeister et al, Proc. of the National Acad. of Sci., 27: 468-474 (1941).

**PROLYSINE**

An amino-acid of dubious constitution, believed to be  $\alpha$ -amino- $\delta$ -hydantoin valeric acid; m.p.  $222^\circ$ .

**PRONTOSIL**

$C_{12}H_{13}O_2N_5HCl$ ; m.p.,  $247-251^\circ$ ; used for treatment of streptococcal and staphylococcal infection, similar to sulfanilamide.

See Chemotherapy.

**PRONTOSIL ALBUM**

See Sulfanilamide.

**PROPHYLAXIS**

Prevention of disease.

**PROSECRETIN**

An inactive precursor of secretin, into which it is transformed by the action of acid.

**PROSTATE**

See Urology.

**PROSTHETIC GROUPS OF PROTEINS**

See Protein Structure.

**PROTAGON**

An extract of brain, probably impure lecithin.

**PROTALBINIC ACID**

A sol containing the sodium salts of the degradation products of albumin by alkali.

**PROTAMINE-INSULIN**

See Insulin.

**PROTAMINES**

In the American classification of proteins, the protamines are simple proteins, soluble in water and other neutral solvents. They are large polypeptides, containing only about 15 peptide linkages, with the preponderance of amino acids being diamines. Therefore the protamines are basic. They precipitate other proteins from aqueous solutions, probably as coacervates. Highly toxic on intravenous injection.

Example: clupeine from herring, scombrine from mackerel.

See Genetics.

**PROTAMINE NUCLEUS HYPOTHESIS**

See Kossel's protamine nucleus hypothesis.

**PROTAMINE-ZINC-INSULIN**

See Insulin.

**PROTEANS**

In the American classification of proteins, the proteans are the first products of hydrolysis of proteins.

The closely resemble the globulins and glutelins.

**PROTECTIVE COLLOID**

A lyophilic colloid adsorbed by a lyophobic colloid, and which acts to stabilize the latter, or vice versa.

**PROTEINASES**

Proteolytic enzymes that attack proteins and peptides of suitable structure. Their point of attack is at the middle of the chain, i.e. at  $-C-N=$ , so that they are called

$\ddot{O}$

endopeptidases. Their action is better in the absence of nearby free amino or carboxyl groups.

**PROTEIN, BENGE-JONES**

See Myelopathic Albumose.

**PROTEIN DERIVATIVES, PRIMARY**

In the American classification of Proteins, those protein derivatives arrived at by hydrolysis, which involve only slight changes in the protein molecule. Insoluble in water and neutral salts, coagulated by heat. Consist of proteans, metaproteins and coagulated proteins.

**PROTEIN DERIVATIVES, SECONDARY**

In the American Classification of Proteins, those hydrolysis products of proteins which represent further cleavage of the protein molecule than in the primary protein derivatives. Soluble in water, not coagulated by heat. Consists of the proteoses, peptones, and peptides.

**PROTEIN METABOLISM IN MENTAL DISEASE**

See Psychiatry, Biochemistry of.

**PROTEINS**

Extremely complex, nitrogen con-

taining organic compounds (or mixtures), found in every living organism and essential to its life. Used largely as the building material for the body, but in times of necessity can be utilized for energy. On hydrolysis with acid, base or enzyme, yield mostly  $\alpha$ -amino acids.

## PROTEINS, ACID AND BASE BINDING BY

Since proteins form colloidal solutions this factor has always made it difficult to study the binding of acid and of base by proteins. Nevertheless, demonstrations have been made of their amphoteric nature in several ways: (1) protein compounds may be precipitated out, e.g. calcium caseinates; (2) proteins may be titrated by dissolving water insoluble substances, e.g. edestin dissolving strychnine; (3) potentiometric titration; (4) compound formation with gaseous bases or acids out of solution; and (5) other physical methods, as measuring electrical conductivity, depression of freezing point which, however, are not clear cut.

## PROTEINS, AMERICAN CLASSIFICATION

A classification recommended by committees of the American Physiological Society and the American Society of Biological Chemists in 1908. It is:

### I. The Simple Proteins

- A. The Albumins
- B. The Globulins
- C. The Glutelins
- D. The Prolamines or Alcohol-Soluble Proteins
- E. The Albuminoids
- F. The Histones
- G. The Protamines

### II. Conjugated Proteins

- A. Nucleoproteins
- B. Glycoproteins or Glucoproteins
- C. Phosphoproteins
- D. Chromoproteins
- E. Lecithoproteins
- F. Lipoproteins

### III. Derived Proteins

- A. Primary Protein Derivatives
  - 1. Coagulated proteins
  - 2. Proteans
  - 3. Metaproteins
- B. Secondary Protein Derivatives
  - 1. Proteoses
  - 2. Peptones
  - 3. Peptides
  - 4. Diketopiperazines

For definitions, see specific entries under above names.

## PROTEINS, AMINO ACID STRUCTURE OF

See Amino Acids, Physiology of.

## PROTEINS, CONJUGATED

In the American Classification of proteins a combination in a form other than a salt of a simple protein with a non-protein group.

## PROTEINS, DERIVED

The various products obtained by the action of acids, enzymes, bases, or heat on proteins, including the hydrolysis products, and the synthetic proteins and polypeptides.

## PROTEIN SPARING

See Carbohydrate Metabolism.

## PROTEINS, PRIMARY DERIVATIVES

In the American Classification of proteins, the primary protein de-

rivatives are those derivatives produced by hydrolysis, which only involve minor changes in the protein molecule.

### PROTEIN STRUCTURE

The protein molecule is a highly complex structure made up of amino acids, and, in some cases, non-amino acid molecules held in very specific arrangement. The amino acids constitute the greater portion of the molecule (in some cases the entire molecule) but the non-amino acid portion, if it is present often plays an important role.

The problem of elucidating the structure of these complex molecules has been approached by two general methods. One is largely analytical and involves the quantitative estimation of the amino acid and non-amino acid molecules making up the larger structure. The other is principally physical and is a consideration of the arrangement of these smaller units and the linkages which are involved. The synthesis of proteins which would furnish absolute proof of structure is so inherently difficult that only minor contributions have been made.

### Protein Analyses

The quantitative analysis of the amino acid content of proteins was the first approach systematically employed, after earlier elementary analyses had yielded little of real importance. The estimation of amino acids is made on protein hydrolysates—usually obtained by the action of acids or bases. The principal shortcomings of this aspect of the problem lie in the probable incomplete knowledge of the amino acids which occur in proteins and the difficulty in devising analytical schemes for those which are known.

There are 25 amino acids whose occurrence in proteins is beyond doubt. Proof of occurrence of at least 22 others is as yet incomplete and there is no reason to believe that even these include all of the naturally occurring amino acids. Satisfactory methods have been devised to determine nine of the amino acids quantitatively. These include cystine, tyrosine, tryptophane, methionine, aspartic acid, arginine, histidine and lysine. Procedures for six other amino acids are less adequate and the remainder can be determined only qualitatively, including those of doubtful occurrence, some of which at least are probably of real occurrence.

Thus we must accept the protein analyses presented in the literature with considerable reservation. There are few proteins for which more than 70% of the amino acids have been accounted for and this fraction includes those amino acids in which the analytical methods are of doubtful value. The amino acids which are undetermined certainly may make no small contribution in determining the structure of the whole.

In spite of the shortcomings of the analyses, they have been used on occasion to estimate the molecular weight of proteins. It is apparent that by using the analysis of one amino acid we may arrive at the minimum molecular weight which will contain one mole of this component. However, to arrive at the true molecular weight we must know the number of times the amino acid occurs in the molecule—a value which cannot be determined by analyses alone. This reasoning has been successfully applied in the case of hemoglobin on the basis of very careful iron determinations.

Assuming one iron atom per molecule a minimum molecular weight of 16,000 was arrived at. Subsequent work showed that there were four iron atoms per molecule—hence the true molecular weight is four times this value.

Bergmann and his co-workers have recently devised an ingenious scheme for calculating the total number of amino acid residues (an amino acid residue is the amino acid minus a molecule of water) in a protein molecule. The method consists of determining the average residue of the amino acids which have been analyzed for and assuming that the remaining amino acids have the same average residue weight. The product of the number of residues and the average residue weight gives the molecular weight.

Bergmann's hypothesis assumes a regular and unvarying periodicity of amino acids in the peptide chain—a line of reasoning for which there is no proof. In addition, he assumed that present analytical determinations are of sufficient accuracy to warrant the type of treatment he employs—a questionable procedure. The further assumption that the remaining amino acids will have no effect on the average residue weight is also open to severe criticism. Bull has employed available data in a new technique to calculate the minimum protein molecular weight which will allow the individual amino acid residues to occur a whole number of times in the molecule. This approach serves only to indicate that there are molecular weights, differing from those required by Bergmann, which fit the data more closely.

#### The Prosthetic Group

As we have indicated earlier,

some proteins have non-amino acid portions constituting the so-called prosthetic group. The nature of this group varies widely. In casein it is thought to be phosphoric acid, in egg albumin and the serum proteins, carbohydrates have been isolated and in intracellular oxidation reduction enzymes it is a porphyrin or flavin group. In proteins such as the latter, the prosthetic group serves a definite purpose, while in other proteins, its significance is more obscure. In all cases the prosthetic group seems to lend stability to the molecule, since removing it makes the protein more labile. The strength of bonding to the protein carrier varies—in some cases it is so tenaciously held that nothing short of hydrolysis of the protein will remove it. In the case of the intracellular oxidation reduction enzymes the prosthetic group can be removed by comparatively mild treatment, apparently without altering the protein component since the two can be recombined to give the original enzyme.

#### The Peptide Linkage

At present, there is no good approach to the question of arrangement of amino acids in the protein. The method of linkage of the amino acids in proteins is, however, well established.

The pioneer research of Fischer and Hofmeister led them to consider the peptide linkage of principal importance in the protein. The linkage is formed by splitting a molecule of water from the carboxyl group of one amino acid and the amino group of the next:



Vickery and Osborne have summarized the very impressive evidence for this type of linkage. How-



ever, certain objections have been raised to the exclusion of other types of linkages, among these are the difference in solubility of proteins and the apparent duplicity of action of proteinases and peptidases in enzymatic hydrolysis of proteins. We will consider these objections after indicating the role of the side chains in determining protein structure.

Since one amino group and one carboxyl group (except for the terminal amino acids in a chain) are involved in the formation of the peptide bond, they do not retain their action as free groups in the native protein molecule. The other portions of the amino acids (R groups or side chains) however are active and are of great importance in determining the chemical and physical characteristics of the chain. These side chains may be divided into two main groups: those having terminal polar groups ( $-\text{COOH}$ ,  $-\text{NH}_2$ , guanidine,  $-\text{SH}$ , etc.) and those having chains which are hydrocarbon in character.

The side chain amino and carboxyl groups may be masked by formation of an amide. The apolar side chains would not be expected to be involved in linkages because of their very character.

The polar side chains determine in large part the acidic and basic properties of the protein. A preponderance of free carboxyl groups gives an acidic character to the protein and a low isoelectric point. Free amino groups make the protein basic and tend to raise the isoelectric point. The attraction and repulsion between these very polar groups along the side chain probably contributes in no small way to the type of folding the pep-

tide chain undergoes. All groups, whether polar or apolar, influence folding because of spatial relations required to accommodate the often massive side chains. Present theories of protein structure give insufficient roles to the R groups. The cystine side chain also plays an important role in bonding between chains. In wool Harris and his co-workers have shown that reduction of the  $-\text{S}-\text{S}-$  groups to  $-\text{SH}$  groups greatly reduces the work required to stretch the fiber and increases its alkali solubility. Both of these findings indicate that the  $-\text{S}-\text{S}-$  groups furnish bonds between the peptide chain.

The difference in solubilities encountered in proteins probably depends in large part on the character of the surface. In all proteins the side chain carboxyl and amino groups seem to be exposed—thus the difference in solubility would seem to depend on the apolar side chains. In a protein such as zein, we may imagine a very hydrophobic surface which would have more attraction for other similar molecules than for water molecules, hence its insolubility in water. The solubility in alcohol can be explained on the greater attraction of the hydrophobic surface for the solvent molecules. In water soluble proteins, the preponderance of polar side chains would give the surface a more hydrophilic character.

The difference in enzyme action on proteins has been shown by Bergmann to be independent of the size of the peptide chain and dependent only on the environment of the peptide linkages. Each enzyme has rather rigid requirements for the amino acid configuration adjacent to the linkages it will split. We can now appreciate the fact



that earlier distinctions drawn between proteinases and peptidases were largely superfluous.

### Molecular Weights

Inasmuch as the arrangement of amino acids in the protein molecule cannot as yet be arrived at—we must content ourselves with a study of the size and shape of the larger structure.

Molecular weight determinations are a direct indication of the size of the protein molecule, since the specific volumes of most proteins fall in a rather narrow range. The specific volume and molecular weights are those of the anhydrous protein molecule and because of the possibility of hydration, may not be the true values for proteins in solution.

One of the best methods for determining molecular weight is by means of the ultracentrifuge, a powerful tool which was largely developed by Svedberg. From the rate of sedimentation of particles in a high uniform gravitational field or the distribution of particles after continued ultracentrifugation, the molecular weight of the particles can be arrived at. Svedberg and his coworkers have determined the molecular weights of a large number of proteins by this technique. One important advantage of the method is that pure preparations of the protein are not required—in a mixture of proteins the molecular weights of each component may be calculated. The principal disadvantage is the complexity of the equipment required.

In his work on proteins, Svedberg was led to believe that the molecular weights of all proteins fall into well defined classes which are simple multiples of 17,500. This

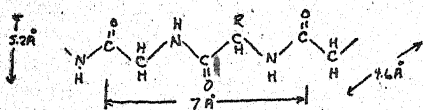
claim has led to more than one theory of protein structure including that of Bergmann which we have discussed. The division of molecular weights into these classes implies some principle which operates in all protein syntheses. The burden is placed either on the synthesizing site itself or on the chemical nature of the amino acids. The great difference in the types of plant and animal tissues in which proteins originate and the variety in the amino acid content of proteins in the same molecular weight class would seem to make such a guiding principle unlikely. There is also considerable scattering of molecular weights around the class weight which would make a statistical study of the theory desirable.

Osmotic pressure measurement on protein solutions is another method of determining molecular weights. If the protein can be isolated in the pure state this probably represents the simplest and most unambiguous method at hand. The work of Adair and collaborators, using this method, is recommended.

The size of protein molecules can also be arrived at by X-ray diffraction studies: The measurements of the unit cell can be made and if the number of molecules in the unit cell can be determined the size of the molecule can be found. Density measurements on the material allow calculation of the molecular weights. Studies are usually made on the hydrated crystals and though this would seem to furnish a method for arriving at the hydration of the protein molecule it is likely that all of the water of hydration does not correspond to the hydration of the protein molecule in solution. The interpretation of X-ray diagrams for globular proteins is rather difficult

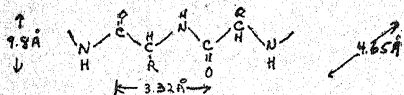
because of their complexity, but this method has yielded valuable results in studies on the simpler fiber proteins.

From X-ray diffraction, Meyer and Mark have rather definitely established the structure of silk fibroin—the simplest of the fiber proteins. They find that an extended peptide chain with a repeating distance of 7 Å units along the chain, a side chain spacing of 5.2 Å units and a backbone spacing of 4.6 Å units will fit the data.



Silk fibroin has a high content of glycine and alanine and the 7 Å units corresponds to a residue of each of these, giving an average value of 3.35 Å units per residue.

Astbury and his workers have studied keratin, the protein of hair and wool. For the stretched hair ( $\beta$ -keratin) they find a peptide chain similar to that of silk fibroin. Because of the presence of side chains of more massive amino acids than glycine and alanine the side chain spacing is increased to 9.8 Å units.



On removing the stretching force the fiber contracts undergoing some type of folding of the peptide chain. The structure of the contracted form ( $\alpha$  keratin) is not well understood as yet.

### Shape

In addition to the size of protein molecules it is also desirable to

study the shapes. The actual shapes cannot be found at present. We can only estimate the asymmetry (ratio of length to width). Because of the lack of knowledge about the true shape we assume as a first approximation that it is a prolate or oblate ellipsoid of revolution. Asymmetry is complicated by the problem of hydration since hydration has the same effect as asymmetry in measurements involving shape. The separation of the two effects has not been made as yet.

The measurement of diffusion constants of proteins can be used to estimate asymmetry. Equations have been derived relating the ratios of experimental diffusion constants to diffusion constants of spheres of the same size and asymmetry. Hydration of the protein would tend to decrease the experimental diffusion constant and hence cause an apparent asymmetry—even if the anhydrous molecule were symmetrical. In most proteins the two factors probably operate simultaneously.

Viscosity has also been used to estimate asymmetry but the presence of a flow gradient greatly complicates the theory in comparison to that of diffusion. A number of equations have been published relating viscosity to asymmetry but no unambiguous derivation has been forthcoming.

Other methods have been utilized in a study of shape: streaming double refraction; the departure of the dispersion curve obtained plotting dielectric constants against frequency, from the Debye curve; and X-ray diffraction studies on crystalline materials. Streaming double refraction requires a high degree of asymmetry and hence is

limited to proteins such as tobacco mosaic virus. Dielectric constant measurements give electrical asymmetry which may or may not be the same as structural asymmetry. The X-ray method serves only for molecules of small asymmetry since very asymmetric molecules will not crystallize in three dimensional crystals.

### Protein Denaturation

Many globular proteins undergo denaturation when treated with agents such as heat, ultraviolet light, X-rays, strong acids and bases, urea, guanidine hydrochloride, alcohol, etc. Denaturation involves four changes in the native protein; (1) decreased solubility, (2) increased viscosity of solution, (3) exposure of oxidizing and reducing groups, (4) large loss of biological specificity.

According to the classical theory of Wu which has been elaborated upon by Pauling and Mirsky denaturation consists of a change from the highly specific structure of the native protein to a more random arrangement in the denatured protein. An understanding of denaturation would probably provide an understanding of protein structure itself.

From studies on surface denatured films in the Langmuir balance further evidence of peptide chains in the native protein have been obtained. Surface denaturation appears to be an unfolding of the coiled peptide chain of the native protein.

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### REFERENCES

Protein Structure: H. B. Bull. *Advances in Enzymology*, I, 1 (1941).

Protein Analysis: H. B. Vickery. "Symposium on Proteins," N. Y. Academy of Sci., February 2, 1940.  
M. Bergmann and C. Niemann, *Science*, 86: 187 (1937).

Peptide Chain: H. B. Vickery and T. B. Osborne. *Physiol. Rev.*, 8: 393 (1928).

The Ultracentrifuge: T. V. Svedberg and K. O. Pedersen, "The Ultracentrifuge," Oxford at the Clarendon Press, New York, 1940.

Fiber Proteins: K. H. Meyer and H. Mark. *Ber.*, 61: 1932 (1928).  
W. T. Astbury and A. Street. *Phil. Trans. Roy. Soc., (London)*, A230: 75 (1931).

Diffusion: N. Neurath. *Chem. Rev.*, 30: 357 (1942).

Viscosity: H. Neurath, G. R. Cooper, J. O. Erickson. *J. Biol. Chem.*, 138: 411 (1941).

Denaturation: H. B. Bull. *Cold Spring Harbor Symposium*, 6: 140 (1938).

### PROTEIN SYNTHESIS

See Autolysis.

### PROTEIN TESTS

See Abderhalden-Schmidt, Acree, Adamkiewicz, Frehden-Goldschmidt, Hopkins-Cole, Lewin, Liebermann, Lipp, Millon, Rosenheim, Salkowski, Vosges-Proskauer.

### PROTEINURIA

The presence of excess protein, particularly albumin and globulin, in the urine. Found in Bright's disease, nephrosis and other febrile conditions, and temporarily after violent exercise.

### PROTEINURIA, ORTHOSTATIC

See Orthostatic Proteinuria.

### PROTEOLYSIS

See Autolysis.

### PROTEOSES

In the American classification of Proteins, those secondary protein derivatives characterized by non-coagulability by heat solubility in

water, and precipitation from solution by saturating half with zinc sulfate; albumoses.

**PROTHROMBIN**

The inactive precursor of thrombin. It is a protein, possibly a globulin.

**PROTocatechuic Acid**

3,4-dihydroxy-benzoic acid, a constituent of tannins and occurring free in the onion.

**PROTOCHORDATA**

Transition forms of chordata which have a notochord but no true backbone.

**PROTocotoin**

Piperonyl-phloroglucinol-dimethyl ester;  $C_{16}H_{14}O_6$ ; crystalline principle from paracoto bark.

**PROTocurarine**

An alkaloid,  $C_{19}H_{24}O_2N$ ; from "pot curare" from *Strychnos castelnaea* Wedd; a powerful poison.

**PROToferrin**

The non-protein portion of catalase.

**PROTONES**

Intermediate products of the hydrolysis of protamines; give strong biuret reaction, more soluble than protamines which they resemble.

**PROTOECTIN**

The member of the group of pectins which is the precursor of the other two members, which see under pectin.

**PROTOECTINASE**

An enzyme that hydrolyzes protopectin away from the cell walls, probably yielding pectin.

**PROTOPINE**

$C_{20}H_{19}O_5N$ ; monoclinic crystals, m.p.  $207^\circ$ , aurichloride is yellow

crystalline powder, m.p.  $198^\circ$ ; fumarine; alkaloid of a large variety of plants, notably *Dicentra spectabilis*, and of opium. In frogs is a narcotic. In mammals causes epileptiform convulsions and circulatory damage. Is also a local anesthetic.

**PROTOPLASM**

Protoplasm is living matter. It is the material basis of life. Whether we have to do with the most primitive forms of life or with highly developed tissues, the living substance within the cells is protoplasm.

The first accurate description of protoplasm was given by Dujardin (1) and von Mohl (2) in the early years of the last century, and what they said of it then is still true today. Protoplasm is a slimy, sticky, and elastic jelly. It takes up water with avidity, but does not dissolve in it. Among familiar substances, that which very closely resembles protoplasm in its purely physical properties is the white of an egg. Both protoplasm and egg-white are soft semi-fluid jellies. Chemically, of course, the two are quite different, yet protoplasm is in large measure made of albumin; indeed, aside from water, proteins are the chief constituents of living matter. The protoplasm of any two cells or organisms is often indistinguishable. Dissimilarities must obviously exist, some of which may be microscopically evident, but the significant dissimilarities, those basic ones which distinguish one organism from another, are not evident. It is the task of the biophysicist and the biochemist to ascertain so far as they can, which protoplasmic properties are common to all living matter and which are specific.

The French zoologist Dujardin is credited with having discovered protoplasm in the year 1835. He called it "sarcode." Undoubtedly, earlier investigators such as the inimitable observer and portrait painter Rösel von Rosenhof, who drew *Amoeba* in 1755, saw the living substance, for that is all there is to an amoeba. However, to Dujardin goes the credit of having first realized that the material he saw is the substance which gives life to a cell.

Usually, protoplasm is organized into small units known as cells. In only a few instances is this not strictly true; the plasmodium of a slime mold is such a case. A slime mold is a relatively undifferentiated mass of living matter, so low in the evolutionary scale that it is neither plant nor animal, but a kind of primordial ooze. Its many nuclei and the large surface it covers rather prohibit regarding it as a single cell, but though not strictly one-celled it is also not multicellular.

#### Chemical Composition

A chemical analysis of protoplasm brings death to it before the experiment is well underway. Consequently, what is ultimately analyzed is not protoplasm, not living matter, but a much changed counterpart. Yet, analyses have been made and with sufficient success to justify regarding the results as a fair indication of the chemical constitution of living matter.

The water content of protoplasm may be accurately ascertained. On an average, living matter is three-fourths water, but the proportion varies greatly. The maximum water content of protoplasm is extraordinarily high. It is as much as 98

per cent in the jelly fish, though one must take care in drawing such a conclusion, for not all of the jelly of this animal is living protoplasm. The water content of man's tissues is 65 to 70 per cent, which is lowered to 53 per cent by old age and disease. A very low value of the water content of protoplasm is to be found in dormant seeds where it may be as low as 10 per cent. If the ten per cent of water in seeds does not represent a minimum for living matter then that of the sclerotium of slime molds certainly does. When winter arrives, or unusual dryness prevails, a slime mold becomes a hard and dry sheet of protoplasm, resembling a stiff bit of paper, often breaking with the brittleness of wood. In this state slime mold protoplasm may live for many years, live, but with no signs of life. Such a sclerotium presents quite a different concept of living protoplasm than commonly held. Given moisture, warmth, and food, the hard, dry, and dormant sclerotium again becomes active protoplasm.

Of the dry weight of protoplasm the greater part is protein and the remainder mostly carbohydrates, fats, and salts.

The composition of the human body is 65 per cent water, 15 per cent protein, 14 per cent fat, 5 per cent salt, and 1 per cent unidentified matter, representing the following elements, in order of abundance: oxygen, carbon, hydrogen, nitrogen, calcium, phosphorus, potassium, sodium, chlorine, sulphur, magnesium, iron, manganese, boron, and others in minute quantities.

For the composition of a slime mold, Kiesel<sup>3</sup> gives the following,

after all water has been abstracted:

	Per cent
Albumin .....	20.65
Plastin (protein).....	8.42
Nucleic acids .....	3.68
Nitrogen-containing extracts.	12.00
Oils .....	17.85
Lecithin .....	4.67
Cholesterin .....	0.58
Carbohydrates .....	8.06
Glycogen .....	15.24
Unknown .....	8.85

#### Methods

##### Microdissection

The simplest way to study protoplasm is to observe it through a microscope, and most of what we know about it has been learned in this way. But the biologist does not stop with what he can see through the microscope alone. He uses accessory methods. Among these is one which has come into wide use; it is micrurgy, the micro-manipulation of exceedingly fine dissection needles, of a micropipette, or microscalpel. By this method it is possible to cut an amoeba in two and observe the behavior of the two halves, the one with and the one without the nucleus. It is also possible by micromanipulative means to cut the neurofibrils of a protozoan such as *Euplotes* and to discover the function of these delicate nerve-like fibers. One of the neatest experiments in micrurgy was done by C. V. Taylor.<sup>4</sup> He was able to isolate the micronucleus of *Euplotes* and by this means discover its function. Fifty-four *Euplotes* were thus operated upon, and none lived more than five days. The absence of the micronucleus is, therefore, not immediately fatal, but without it *Euplotes* can neither

eat nor reproduce. The organism lives only as long as the food within it lasts.

##### Dark-field

An important accessory to microscopic work on protoplasm is that involving the use of special means of illumination. There are numerous ways of illuminating microscopic matter, one of the most interesting being dark-field. The method originated in the colloid chemical field where it is necessary to reveal particles which are below the limit of microscopic visibility. The colloidal matter is viewed against a black background and illuminated laterally. The method is fascinating, but one has to be exceedingly cautious in judging the picture seen, for diffraction phenomena are involved and may obscure the true picture.

##### Ultraviolet Microscopy

The microscope has a limit, fixed not by the magnifying power of lenses, but by the wave length of light and other factors which determine the resolving power of lenses. The highest powers of the microscope reveal objects which are about 0.1  $\mu$  in size. Greater magnification could be obtained, but it would be of no use, because it would then be impossible to distinguish between two lines which are closer together than the length of the wave of light used. It is not greater magnification, but greater resolving power that is needed.

As the resolving power of a lens is proportional to its numerical aperture and inversely proportional to the wave length of the light used, ultraviolet light, having short wave lengths, should increase resolving power. The use of it has given



rise to the ultraviolet microscope.

By using ultraviolet light with a wave length of 275  $\mu$ , as compared with 550  $\mu$ , the average wave length of white light, it is possible practically to double the resolving power of the lens. The theoretical limit of the resolving power of an objective of numerical aperture 1.40, is 0.6  $\mu$  for a wave length of 450  $\mu$ , and 0.13  $\mu$  for a wave length of 365  $\mu$ . This value of 0.13  $\mu$  is slightly above the lower limit of microscopic visibility. An objective of numerical aperture 1.40, with the 365  $\mu$  ultraviolet spectral line (of mercury) will give 19 per cent more resolving power than the best microscopic system with white light. But there are difficulties. Glass is practically opaque to light waves of less than 300  $\mu$ , i.e., to ultraviolet light; furthermore, such light is invisible to the human eye. The first difficulty is overcome by using quartz lenses, and the second by substituting the photographic plate for the human eye.

With the ultraviolet microscope, magnifications of 5000 diameters result in sharp brilliant images and a degree of resolution surpassing that achieved by any other known optical system. With such an equipment some excellent photographs of living cells have been taken.

Any wave length shorter than the average of white light will increase the resolving power of a lens. Consequently, light just beyond the visible limit of the violet end of the spectrum (the visible spectrum stops at about 390  $\mu$ ) should be better than white light, and it retains the advantage of white light in passing through glass. Ultraviolet of 365  $\mu$  is, therefore, used with glass lenses.

Difficulties have retarded the use of this method. Thus, ultraviolet light may harm living cells. Certain microorganisms are destroyed almost instantly by ultraviolet light; others are mildly excited, and still others remain normal.

### Model Making

To make a model is an instructive way to visualize a mechanism. In fact, Lord Kelvin thought it the only way. By observing the behavior of drops of mercury, of oil, and of silica mixtures, scientists have imitated the behavior of cells, in particular amoeba. A familiar experiment of this kind is that involving a drop of chloroform under water. Although the drop will not at first take in a piece of glass, if the glass is coated with shellac it is immediately engulfed. After "digesting" or dissolving off the shellac, the chloroform ejects the glass. A living amoeba does the same, i.e. it ingests particles which are not food, such as carmine particles, and immediately gives them off. The three phenomena, a living amoeba eating real food (organic matter), a living amoeba eating imitation food (carmine), and an imitation amoeba (a chloroform droplet) "eating" imitation food may all be due to the same force, viz., a change in surface tension.

Other forms of artificial cells have been made. Thimbles of porous clay or cellulose have been impregnated with agar, then dipped in pectin, in imitation of the root-hair with its pectin layer. The inner surface of the wall of the artificial cell was coated with fatty substances such as lecithin and cholesterol, and, finally, a layer of "protoplasm" was added, of agar or gelatin and proteins. Such a cell imitates the

selective permeability of living tissue.

A study of the distribution of magnets floating on water was made in an attempt to explain the orientation of chromosomes in cells.

Model making in an attempt to imitate the living cell is to be commended, but it must be remembered that the model bears only a feeble resemblance to the living cell and may imitate what happens but not how it happens.

#### Osmosis vs. Imbibition

Zoologists regard Claude Bernard as the father of modern physiology, but botanists give this honor to Wilhelm Pfeffer. Actually, it was the time in which the men lived rather than the men themselves. In 1877 Pfeffer presented his classical "*Osmotische Untersuchungen*."<sup>5</sup> These studies involved the phenomenon known as plasmolysis, or the shrinking of a cell due to loss of water. Nowhere in science is there a more dramatic series of events than those which led from a simple botanical experiment in plasmolysis to the laws of solutions. Naegeli discovered the selective permeability of the plasma membrane; deVries formulated the principles underlying it; Pfeffer determined the pressures developed by plant cells; van't Hoff enunciated the solution laws; and Arrhenius set forth the dissociation theory out of which arose the science of electrochemistry.

It is not necessary here to go into a discussion of so well known a force as osmosis, but there is one important feature of it in connection with protoplasm which should be mentioned.

A plant cell has a large central

vacuole, the contents of which is a solution of non-living matter. There is no question as to the method by means of which water enters this central sac. It is by osmosis. The kidney is also an osmotic mechanism. If protoplasm itself, aside from its vacuoles, takes up water, it may be by osmosis, in which case protoplasm is a solution in a sac, the latter being the cell membrane, or the protoplasm may absorb water by imbibition, in which case protoplasm is a jelly. There are many reasons why protoplasm cannot be regarded as a solution, for example, it is elastic, it is not soluble in its own aqueous medium, and it clings together. Viewed as a jelly, the entrance of water into protoplasm is by imbibition and not by osmosis. This would appear to involve a controversy. Possibly the supporters of the two opposing views are arguing at cross ends. As J. Loeb<sup>16</sup> put it, "the reason that osmotic pressure, the viscosity of protein solutions, and the swelling of protein gels are all influenced in a similar way by electrolytes is that all three properties are in the last analysis functions of one and the same property, namely, osmotic pressure." Loeb applied the Donnan equilibrium. There is no questioning the Donnan equilibrium, for it rests on thermodynamical reasoning, first advanced by Willard Gibbs. The equation holds under ideal conditions, but tissues contain sugar and the molecular osmotic effect of sugar in high concentration is sufficient to upset ionic electrical equilibria such as postulated by Donnan.

Whatever position one may take in the osmosis vs. imbibition controversy, several facts remain clear; protoplasm is not a true solution,

and it is not soluble in water.

#### Permeability

One of the most remarkable properties of protoplasm is its capacity to control the entrance and exit of substances. This property is known as selective or semi-permeability. Selective permeability presumably rests on special properties of the plasma membrane. That cells possess membranes, delicate outer protoplasmic layers differentiated from the inner protoplasm, is generally accepted as fact. Microdissection methods have revealed thin films on cells, on amoeba and erythrocytes<sup>7</sup> with sufficient certainty to settle the question of protoplasmic membranes in the affirmative. The nature of this membrane has been much discussed. I should here like to emphasize one important feature of cell membranes, especially amoeboid cells, though not restricted to them, namely, that the plasma membrane is living and of a changeable nature. This is best illustrated by the faulty deduction of one of my students, who, seeing the protoplasm at the surface of a cell in motion, concluded that as the outer protoplasmic layer was flowing there could be no membrane there. The truth of the matter is that the membrane is protoplasm, capable of the same activities as the inner protoplasm.

So numerous have been hypotheses on selective cell permeability that the conclusions which can be drawn with confidence are few. But some facts are beyond question: thus, fat solvents enter very rapidly and salts slowly. Sodium increases the permeability of the protoplasmic membrane and calcium decreases it; within a restricted group, sugars enter cells according to the size of their molecules, but among other

sugars and some dyes the larger molecules enter more readily than certain smaller ones.

Overton explained the rapid entrance of fat solvents such as alcohol, ether, and chloroform, on the valid assumption that the cell surface is fatty in nature; he suggested that "lipoids," lecithin and cholesterol, are concentrated there. Subsequent work has substantiated this. But microdissection reveals a more substantial layer on cells, not just an oil film. In all probability the plasma membrane is of protein with a thin coating of fat; it is above all, living matter, an intimate part of the inner protoplasm.

Loeb was inclined to group the elements to which protoplasm is permeable or impermeable on the basis of valence, and to predict that if one monovalent cation, such as sodium, affects protoplasm in one way, another monovalent cation, such as potassium or lithium, will do the same. He also assumed that bivalent ions, such as calcium, magnesium, or barium, will affect protoplasm alike. There appears to be some justification for this in the behavior of a non-living system such as gelatin, but with living matter the rule does not hold. Brooks<sup>8</sup> and others found that monovalent sodium and bivalent magnesium both increase the permeability of sea-urchin eggs in dye-stuffs, whereas bivalent calcium decreases it, that monovalent sodium and bivalent magnesium have identical effects upon protoplasm, that these metals increase the permeability of animal cells, but decrease the permeability of plant cells. These experimental facts indicate the danger of drawing all-inclusive deductions. After all, why should an animal egg react to a

salt in the same way as does a plant cell? The reactions of the two may be the same, for cells wherever found have certain characteristics in common, but they may also differ as widely as do the plants and animals of which they are a part.

The problems of permeability are many. One of the most interesting is the accumulation of substances within the cell at a concentration greatly in excess of that in the surrounding solution. The freshwater alga *Nitella* lives in pond water where the amount of potassium is very slight, yet potassium may occur within the cell sap at a concentration one thousand times that of the potassium in the surrounding water.

The marine alga *Valonia* is a one-celled, bladder-like plant, two or three centimeters in diameter, with a large central vacuole containing several cubic centimeters of sap. The contents of a number of cells yield sufficient sap to permit an accurate chemical analysis. The results show that the concentration of potassium is over forty times as great within the *Valonia* cell as without, whereas sodium is only one-fifth and calcium one-seventh as concentrated within the cell as in the sea-water. Starfish and sea-urchin eggs, and many other cells contain a higher concentration of potassium than of sodium, though this relationship is reversed in sea water.

Most extraordinary is the contrast in the behavior of *Valonia* and its close relative *Halicystis*. Analysis of the sap of this latter alga reveals that instead of there being five times as much potassium as sodium within the cell as in the case of *Valonia*, there is eighty-

seven times as much sodium as potassium. Should such differences in ionic concentration remain constant, they could be used to distinguish species, especially where morphological differences are slight. We should then have a classification of plants based on chemical or physiological distinctions.

#### Electrical Forces

The role of electricity in the living world is a tempting study.<sup>9</sup> It is hardly possible to escape the conclusion that electric forces are involved in life processes, but little is known of how they play their part. Where we deal with uncertain predictions, it is well to start with what is known. No one questions the existence and magnitude of the electric shock administered by certain organisms, of which the ray fish and the electric eel are well known examples. Both are capable of delivering very high potentials. *Gymnotus*, the South American eel, is said to yield a maximum of 1,000 volts, sufficient to fell moderately large animals. The presence of a potential in the ray may be demonstrated by allowing the fish to rest upon a metal plate with another plate upon him. If the two plates are connected to a group of students, a bell, or a low voltage electric lamp, and the ray angered by twisting its tail, a substantial shock will be felt by the students, the bell will ring, or the light burn. On occasion, a 6-volt electric-light bulb may be burned out by the excessive voltage of the ray.

The most extraordinary feature of these high potentials in living systems is the fact that nature is here producing voltages of a magnitude that cannot possibly be dupli-

cated in the laboratory without metals, and we have no knowledge of the means by which nature accomplishes this.

The foregoing potentials are the totals of thousands of feeble cell potentials, and these latter are probably membrane potentials. Many non-living and all living membranes are selectively permeable. Thus, parchment paper and collodion membranes permit positive ions to pass through more readily than negative ones. The apple skin is likewise more freely permeable to the cation potassium than to the anion chlorine. When a selectively permeable membrane separates electrolytic solutions, there results a distribution of ions on the two sides of the membrane which differs from that existing at the beginning of the experiment. The values are usually of the order of 50 mv.

That living cells are generators of electromotive forces is shown by staining methods. Basic dyes which ionize as  $R^+$  and  $Cl^-$ , stain the nucleus more readily than they do the cytoplasm. The nucleus is, therefore, electronegative, because it adsorbs the positive or color ion  $R^+$  of the dye. Cytoplasm, on the other hand, stains better with acid dyes which ionize as  $H^+$  and  $R^-$ . It is, therefore, less negative than the nucleus, i.e., electropositive in reference to the nucleus. Similar evidence leads to the conclusion that the nucleolus is less negative than the nucleus. The cell is thus a system with a more positive nucleolus, a negative nucleus, and a more positive cytoplasm. The outer solution which bathes the cell also differs electrically from the cell protoplasm. This means that differences in electrical potential exist

between nucleolus, nucleus, cytoplasm, and external medium. The living cell is thus an accumulator, that is to say, an electric storage cell in which the nucleus is the cathode.

Membrane potentials are but one source of electric forces in tissues. Oxidation-reduction potentials, concentration potentials, and diffusion potentials are other possible sources of electromotive forces in living matter. The first of these may be of considerable biological significance, especially in nerve conduction.

It is not always possible to state whether or not electric potentials measured in living systems are real or are set up by the experiment, but enough work has been done to indicate a close correlation between the potentials measured and accompanying life processes. Thus, Harvey<sup>10</sup> and others have correlated brain potentials with the state of the human mind during sleep.

The foregoing discussion has to do with electricity involving a flow of current. There is yet another kind of electric forces, those which Freundlich<sup>11</sup> called electrokinetics, a group term for all colloidal electrical phenomena. If colloidal particles or living cells are freely suspended in an aqueous medium they will migrate toward one pole or the other when subjected to the influence of an electric field. They must, therefore, possess an electrical charge.

Among the four forms of movement having to do with colloidal matter, that of cataphoresis, or electrophoresis, gives most promise from the biological point of view; at least it has yielded some convincing experimental results. Electroendosmosis may also play a role in



life, for example, in determining the one-way flow of water through the intestine wall.

One of the most significant experiments yet done in physiological electrokinetics is that of Moyer<sup>12</sup> who ascertained plant kinships on the basis of the electrophoretic behavior of latex particles.

The discovery of Landsteiner<sup>13</sup> that there are four distinct types of blood in man and that these types can be determined by coagulation tests, and the relationship known to exist between the blood of man and that of apes, as determined by coagulation, led Moyer<sup>12</sup> to seek a species relationship on the basis of isoelectric points and mobility curves.

When a stem of *Euphorbia* is cut, it exudes latex which is a fine suspension of hydrocarbon in an aqueous medium of salts, carbohydrates, and proteins. The rate of migration of latex particles under the influence of an electric field, and their isoelectric points are determined by the protein or other substance which coats them. If the surface layer is protein, it may show the same specificity in regard to genera as do the proteins in blood. Moyer established migration curves by plotting rate of mobility against acidity.

The curves of several species of *Euphorbia* showed a remarkable relationship. Those species known to be taxonomically related, as established by the time-honored methods of plant classification, yielded cataphoretic migration curves of identical form which crossed the line of no migration at almost precisely the same pH value; i.e., they had the same isoelectric points; whereas those species taxonomically

not closely related yielded curves of different form, with other isoelectric points. An occasional species, which did not fall into any group, proved to be an isolated form of questionable relationship on taxonomic grounds. Further study brought other interesting facts to light. The geographic distribution of the species was such as to agree with the protein relationship, and chromosome numbers showed similar conformity.

### Viscosity

The viscosity of protoplasm runs the whole range of possibilities except the lowest, for protoplasm is never as thin as water or probably ever below 25 times water which is about the consistency of sulphuric acid. The usual average viscosity of active protoplasm is somewhere near that of glycerine which is 860. As protoplasm may become solid its maximum viscosity value is infinite. The consistency of protoplasm is constantly changing when a cell is metabolically active.

The ways of measuring protoplasmic viscosity are numerous and ingenious; they include the shape of the protoplast after plasmolysis; the rate of fall of starch grains within the cell when the position of the cell is reversed; the centrifugal force required to stratify the protoplasmic granules—these last two methods involve Stokes' formula; the amplitude of the Brownian movement of particles suspended in the protoplasm; the rate of travel of a minute metal particle placed in the protoplasm and magnetically attracted; the microdissection of protoplasm in which the consistency is judged by the time required for a furrow or other deformation to be eradicated. The last method



though rather inexact is yet the only one which permits determining the viscosity of a small region of a cell such as the nucleus. All methods show an extraordinary variability of the viscosity of protoplasm.

From a structural viewpoint the anomalous viscosity of protoplasm is particularly significant. In 1685 Isaac Newton announced, in his "Principia," the law of fluid flow. He expressed it mathematically thus:  $v = \phi Fr$ , which means that the velocity, or rate of flow,  $v$  is proportional to the fluidity  $\phi$  (the reciprocal of the viscosity) and the shearing stress  $F$  on either of two planes separated from each other by the distance  $r$ . It remained for Jean Poiseuille, French professor of medical physics, to furnish proof of Newton's law. He found that the volume of flow of a liquid  $v$  is proportional to the time  $t$ , the pressure  $p$ , the fourth power of the radius of the capillary  $r$ , and a constant  $k$ , and inversely proportional to the length of the tube  $l$ . This relationship he expressed in the following formula which bears his name,

$$v = \pi pr^4 t / 8l\eta$$

Pure liquids and true solutions all obey Poiseuille's law and are said to be Newtonian, that is to say, to exhibit true viscous flow. But many solutions do not obey the law; they are non-Newtonian and exhibit anomalous flow. They possess not one viscosity value but an infinite number of values.

Another characteristic of non-Newtonian liquids is the possession of a yield value, which means that an initial stress must be exerted in order to start flow.

Non-Newtonian behavior and

yield value are indicators of molecular aggregation, of structural features, such as account for elastic properties, which suggests that we may be dealing with two kinds of viscosity, true viscosity or inner friction, and structural viscosity. The significance of this becomes apparent when structure is considered.

### Elasticity

The elasticity of protoplasm is obvious in many ways. An easy way to demonstrate it is to stretch protoplasm between needles mechanically controlled. It may be drawn out into very long thin strands.

Scarsh<sup>14</sup> has emphasized the elastic qualities of protoplasm as the most reliable criterion we have of the structure of living matter. He makes the following important observation. Strands of streaming protoplasm may be so rigid that when slowly stretched, by swelling in water, they suddenly snap, and then crumple up on the recoil like a solid thread and not like a fluid; yet, almost immediately they show fluid properties again in that the protoplasm begins to stream.

Another demonstration of the highly elastic qualities of protoplasm not involving artificial means is the snapping and rapid contraction of cell processes such as pseudopodia and protoplasmic threads, naturally formed by cells. This is to be seen in tissue cultures where fibroblasts form long protoplasmic streamers which adhere to the glass as the cell moves forward, then stretch and snap.

### Structure

The structure of protoplasm is of two main categories, that which is

microscopically visible, and that which lies beyond the powers of the microscope. A presentation of the first involves simply a description of what is seen; an account of the second is purely interpretive though based on known facts.

Protoplasm, from what is seen through the microscope, has been called a granular suspension, an emulsion, a symmetrical pattern of alveoli, an entanglement of fibers, and a three-dimensional net. At times, and under certain conditions, all of these exist, but several are merely different forms of the same thing, and others are based on fixed and stained material which may contain artifacts. Ordinarily, the picture presented by living protoplasm is that of a heterogeneous collection of globules; in short, an emulsion. When the globules are of the same size and under pressure, a symmetrical arrangement of dodecahedra or tetrakaidecahedra is obtained. The pattern of this structure in cross section is one of hexagons, and was termed alveolar by Bütschli. The structure is merely a special form of the protoplasmic emulsion.

The emulsion in protoplasm is not without significance, for the dispersed fat globules serve as reserve food material. But this optically visible structure tells nothing of the basic nature of living matter. If a physical property of protoplasm such as elasticity is selected and a structural interpretation of it attempted, it becomes immediately evident that the visible emulsion has no bearing on the problem. The same is true of most other characteristic properties of living matter and organic substances in general. Thus, when milk coagulates the visible emulsion of butter fat plays

no part, it is the casein in milk which coagulates.

The ultramicroscopic structure of protoplasm can only be postulated, but the postulates are well founded, for proteins are the basic material of protoplasm, and of the structure of proteins much is known.

Emil Fischer regarded the proteins as taking part, in one way or another, in all physiological processes in the living organism; and Pauli<sup>15</sup> says, "there can be no doubt as to the central position of the proteins in the organization of living matter. They alone display the specific properties of life."

The basic unit of all proteins is now known to be the polypeptide chain or its simpler units the amino acids. The structural formula of these is the chain,  $\text{-CO-NH-CH-CO-}$ . Attached to the CH radicals are side chains by means of which it is possible to join laterally a number of the longer main chains at various points. The linear unit, and the side linkages are two very important properties of protein structure.

In general, nature builds with fibrous structural units. Trees sway in the wind and withstand tremendous pressures without breaking because their cellulose is made of long tenuous fibers. The cellulose fiber has been shown by Sponsler<sup>16</sup> and others to be a long chain of anhydrous glucose units.

With protein fibers as structural units it is possible to postulate a number of mechanisms which will satisfy the demands of the physical properties of protoplasm. Thus, an entanglement of fibers, a molecular brush heap, will satisfy the elastic qualities which are so typical of jellies and of protoplasm. A brush heap is elastic, a sand pile not.

Quite some time before chemists had progressed this far with their theories of protein structure the botanist Naegeli had postulated a micellar structure of jellies. Micellae are molecular aggregates, that is to say, colloidal particles. In cellulose, the micellae either touch and adhere or are embedded in a common matrix. Such a structure is essentially a granular one. When micellae are symmetrically arranged they are presumed to resemble bricks in a wall.

There is much evidence to support heterogeneity in the structure of cellulose, proteins, and organic tissues enough to counteract the tendency to get away from the micellar theory. One can by no means discard it altogether.

That property of organic matter which was most damaging to the micellar hypothesis was tensile strength. A structure of isolated units is not likely to possess great strength. The first step taken toward a more satisfactory accounting of the tensile strength in organic substances was the overlapping of the fibrils, but symmetrically arranged overlapping fibers would, if uniformly distributed, eliminate micellae. The low tensile strength of cotton as compared with the high tensile strength of flax suggests that the overlapping of fibrils is more complete in the latter than in the former, that is to say, discontinuity is responsible for low tensile strength.

Whether, and when, the structural unit is a micel, a molecular aggregate, or a molecular fiber cannot be said with certainty. Elasticity indicates that the structural units are scattered if the material is of low tensile strength, as is cellophane,

but are arranged in an orderly manner with overlapping if the material is of high tensile strength as is ramie fiber.

Out of the numerous facts and suggestions so far considered, the most significant is the recognition that the structural unit of elastic jellies is a fiber. This is a great gain over older concepts in which granules and globules were the structural units of protoplasm and gels.

One important and difficult task still confronts us, that of postulating a structure which possesses the capacity to flow freely yet is capable of exhibiting elasticity, rigidity, tensile strength, and similar properties characteristic of solids. The interpretation of a structure possessing both fluidity and rigidity, has been nicely accomplished by the protein chemists. The earliest suggestions of this kind arose in the minds of workers active in the colloidal and textile fields of research; they included Herbert Freundlich, Fritz Haber, Herzog, and others in Europe, and Sponsler<sup>17</sup> in America. It was while associated with these chemists that I applied to protoplasm their concepts of gel structure. I<sup>18</sup> put the matter this way: A structural configuration of long protein chains with unsatisfied lateral bonds giving weak unions at specific points along the chain meets the requirements of a brush heap of loose construction which will allow for a mechanical interpretation of fluidity in an elastic system.

I thus laid emphasis on the linear protein molecule, on side linkages and occasional weak bonds, as the structural organization of protoplasm. At about the same time

Kurt Meyer<sup>10</sup> independently advanced a similar hypothesis but carried it one step further. He, and H. Mark<sup>20</sup> pointed out that there are two types of proteins, fibrillar and globular ones. Meyer and Mark demonstrated the undoubted presence of fibrous molecules in silk, sinew, and stretched muscle. From this it followed that the living substance is composed of a network of primary valence chains which at several points are coated by a hydrated layer, and at other points are tied together by chemical bridges held by molecular cohesion; today one would say residual valences or hydrogen bonds. Later, Banga and Szent-Györgyi<sup>21</sup> enlarged the hypothesis slightly. They stated that whenever nature needs a mobile protein such as serum albumin, globulin, secretions like milk-proteins, enzymes, and hormones such as insulin, it applies the globular shape, and whenever it wants to build a solid structure it applies the rod shape. And they add that "Proteins have been found to be mostly globular because unconsciously the mobile and more easily accessible proteins have been selected for study." It should be remembered, however, that among the earlier workers on proteins the polypeptide chain was foremost in their minds, so I should say that the fibrous proteins came first and later the globular ones. Today the structural nature of globular proteins is otherwise interpreted. It is now generally agreed that the "spherical" protein molecule is not actually such, but is a much folded chain.

With the foregoing information as a background, we can proceed with our problem. We are concerned with interpreting the structure of a system which possesses

such solid properties as elasticity yet is capable of flow. The presence in organic systems of fluidity and structural continuity is readily satisfied by assuming that one of the bonds of the side chains which establishes lateral connections is a feeble bond. It has been suggested that variations in the degree of hydration of the side chains constitute a possible explanation of a weak attachment at one end, but a better interpretation of this feeble union is that given by the hydrogen bond.

In a chemical cycle, as in muscle, during which accessory molecules go in and out of combination with the side chains of the protein main chains, the latter take up a cycle of configurations. In all such dynamic systems, of which protoplasm is one, there is a constant shifting of ties between the structural units. The loose union which permits this is very probably a hydrogen bond. Linus Pauling<sup>25</sup> believes this bond to be of greater significance for physiology than any other single structural feature. It serves our present purpose well because it is not a strong bond.

When an atom of hydrogen is attached not to one but to two other atoms and thus acts as a tie between them, the union involves the hydrogen bond. In such a case, one of the points of attachment is a firm covalent bond, and the other a weaker one, essentially ionic in character. The latter is the hydrogen bond.

Water illustrates the situation well; fluidity there depends upon the shift which takes place between one molecule and another. Water molecules are always in partnership, but always changing partners. When solutions yield diffraction pattern, it is indicative of a definite

degree of symmetry in arrangement.

Pauling<sup>22</sup> interprets the structural continuity of water in terms of the hydrogen bond. Instead of the classical  $H_2O$  it is presumed that each oxygen in water is surrounded by four hydrogens, two of which, close to the oxygen atoms, are joined to it by primary valences, and two, farther away, by the hydrogen bond.

The situation existing in water is even more applicable to proteins where structural possibilities are infinitely greater; and proteins are the building material of protoplasm. In amino acids the nitrogen atom has one open coordinate position with which it may unite to a hydrogen in the same or another molecule. This union is a hydrogen bond; it may join the nitrogens of two amino acids,

It is thus evident that the hydrogen bond provides a mechanism by means of which the coexistence of continuity in structure, elasticity, rapid changes in viscosity, and fluidity in protoplasm may be explained.

One more property of the protein chain must be considered for it is the basis of one of the most characteristic properties of protoplasm, namely, contractility. That feature of the linear protein molecule which is mechanically responsible for contractility is its folded form. A macroscopic change in form, such as muscular contraction, is accompanied by a change in form of protein chains; consequently, visible contraction and elongation in muscle or protoplasm is to be ascribed to the contraction and relaxation of fibrous protein molecules, which in turn are controlled by chemical activities. The tendency of rubber-

like matter to take its original form after deformation can be ascribed to the fact that the chain molecules themselves are capable of deformation, and that adjacent chains slide one over the other just as do molecules in a viscous fluid.

From such suggestions arose the hypothesis of the folded polypeptide chain, as recently set forth anew by Atsbury.<sup>23</sup> According to Astbury fibrous proteins such as keratin when unstretched occur in the folded or  $\alpha$  state. On stretching, the fiber becomes completely extended and then exists as  $\beta$  keratin.

The situation is somewhat more complex because, as Astbury<sup>24</sup> states, the fibers are so formed as to form a grid. A parallel alignment of grids results in a three-dimensional lattice, or crystal.

#### Streaming

Metabolically active protoplasm is in a constant state of motion. Sometimes this motion is a feeble turbulent one and sometimes it takes the form of a rapid current, called streaming or cyclosis. The protoplasm of some cells is intermittently active and of others incessantly so. The latter is true of the *Myxomycetes* or slime molds.

The function of protoplasmic movement, other than when involved in locomotion has long been the subject of discussion.<sup>25</sup> But what concerns us as biochemists and biophysicists is not function but the mechanism responsible for the streaming.

So baffled have scientists been by the constant movement of protoplasm that they have resorted to every known force to explain it. Thirty years ago surface tension dominated biological thought. Rare



was the vital process which escaped interpretation in terms of surface forces, and protoplasmic streaming was no exception. Just how this form of energy was supposed to cause the flow of protoplasm was not made clear; perhaps by a constriction passing in wave-like manner along a protoplasmic thread. It would be difficult to account for protoplasmic flow in an *Amoeba* on this basis. Besides, there is no evidence to support it.

Next came the suggestion that the one-way or shuttle type of flow in certain lowly plants where movement is first in one direction and then in the other, may be due to hydration at one end and dehydration at the other end. But the protoplasm flows equally well in both directions, and when fully submerged. Obviously, dehydration by the atmosphere can play no primary part.

Many cellular activities find their counterpart in colloidal phenomena. There thus arose the suggestion that protoplasmic streaming is an electrophoretic migration of particles, or an electroendosmotic flow of the aqueous medium; if either, it is the latter, for in streaming protoplasm the entire mass of material moves and not just the suspended particles.<sup>7</sup> In spite of some attempts to prove that streaming protoplasm is associated with electric potentials, the evidence is not conclusive that the potentials measured are real in the sense of innate to the protoplasm, and if real, are the cause rather than the result of the streaming.

None of the foregoing theories of the mechanism of protoplasmic streaming can be regarded as convincing.

When a moving picture of a slime

mold is taken at one-eightieth of the normal speed and projected at the usual rate, the entire plasmodium or protoplasmic mass is seen to go through rhythmic contractions and expansions similar to the pulsations of the heart. At each contraction and expansion the direction of flow reverses. Contractility and flow are thus perfectly synchronized. With outgoing protoplasm there is contraction, with incoming protoplasm, expansion. The mechanism of protoplasmic movement in slime molds is, then, one of rhythmic contraction and relaxation of the plasmodium as a whole.<sup>26</sup> The contractions and expansions alternately force and pull the more fluid inner protoplasm back and forth. The pulsation frequency is once every 45 to 50 seconds.

When first ascribing the outward and inward flow of protoplasm in slime molds to rhythmic pulsations of the plasmodium, I gave no hint of the possible mechanism of the rhythm, of the systolic and diastolic movements. It later<sup>27</sup> occurred to me that these movements may be due to a rhythmic contraction and relaxation of folded molecules, such as those postulated by Astbury.<sup>28</sup>

The energy for this work is supplied by the oxidative processes of the cell.

Protoplasmic flow must involve pressure. Kamiya<sup>29</sup> set about to measure it, to ascertain, as it were, the horse-power of the protoplasmic machine. He placed a double-lobed bit of slime mold protoplasm in a moisture-chamber of two compartments separated by an agar wall. The strand of protoplasm connecting the two lobes passed through the agar wall thus leaving one lobe in each hermetically sealed com-



partment. One of the compartments was kept at constant atmospheric pressure, whereas the pressure in the other compartment was under control.

When the pressure in the two compartments is the same, the shuttle movement of the protoplasm goes on normally, but if a difference in air pressure is established between the two compartments, the movement of the protoplasm in the connecting strand is strikingly affected. A slightly reduced pressure in one of the compartments hastens the flow of the protoplasm through the connecting strand into that compartment. A slightly higher pressure retards the flow of protoplasm through the connecting strand into that compartment. If the pressure applied is stronger than the motive force developed in the plasmodium, then the forward moving protoplasm is forced backwards. The direction and velocity of the protoplasmic movement in the connecting strand can thus be accurately controlled.

The precise artificially applied pressure necessary to hold the protoplasm at a standstill is equal to the vital motive force responsible for protoplasmic flow. The range of this pressure is between  $\pm 20$  cm. of water. The maximum absolute value encountered was 28 cm. of water.

As the rate of protoplasmic streaming is constantly changing, the motive force also changes, and the applied balance-pressure must be adjusted accordingly, if the protoplasm is to be kept immobile. By plotting pressure as ordinates against time as abscissas, undulating curves are obtained which faithfully portray the distinguishing

features of the changes which the motive force undergoes during the rhythmic succession of vital processes.<sup>30</sup> The graphs obtained give a complete picture of the rhythm in protoplasmic activity. Characteristics, such as wave form, frequency, polarity, and amplitude are portrayed by the curves.

#### Rhythm

That contractility is a widespread property of living matter is generally recognized, but not much appreciated is the equally widespread potential capacity for rhythmic contractility in tissues. Certain examples of this are all too familiar. Heart muscles contract rhythmically. The muscles of the diaphragm are induced to do so. Contractility occurs periodically as peristalsis in the walls of the intestines, the tube. Feeble uterine contractility is thought by some to be continuous. Voluntary muscles are likewise believed to undergo rhythmic contractility during periods of apparent rest. The bladder, not functionally contractile, can be experimentally made to pulsate rhythmically.

Rhythm in the nervous control of organisms has long been known and has received added confirmation of late in work involving the electric recording of rhythmic waves from the brain.<sup>10</sup> That a rhythmic train of events in the nervous system regulates certain body functions is shown by the rhythmic movement of the respiratory muscles where the activity is not intrinsic as in the case of the heart. Such induced rhythms are controlled by periodically recurring stimuli from the medulla. When the action of a single neuron is studied a clear record of periodic neural impulses is obtained, which recur in perfect rhythm.

The references so far, other than that to slime molds, have had to do with multicellular organisms, with tissues; but individual cells, whether organisms or from tissue, pulsate rhythmically. Warren H. Lewis<sup>31</sup> has observed the pulsation of a single cell from chick heart muscle in culture. The pulsation of a heart is the expression of the many pulsations of its cells which may not be in perfect synchronism with each other, the heart rhythm being merely the resultant.

Rhythmic movements are common in lower organisms. Kamiya gives an interesting case of it in *Euglena*. When this Protozoan is treated with certain reagents, notably acids, it undergoes rhythmic peristaltic movements. The pulsation is induced, but the capacity to undergo contractile motions and the rhythmicity are innate qualities.

All nature is rhythmic. In animate nature the visible instances of it are but outward signs of the basic rhythm in protoplasm. The rhythmic contractility of slime mold protoplasm is but one instance of a very widespread phenomenon. In my belief, all protoplasm is capable of rhythmic contraction, but ordinarily exhibits it only in those tissues where it is functional.

Some modern workers are inclined to strip protoplasm of the properties of multicellular organisms, forgetting that the attributes of higher forms of life exist because they are properties of protoplasm. The protoplasm of primitive organisms is not less intricate, less responsive, nor less organized, than that of higher forms of life. It is fallacious to hold that primitive protoplasm is devoid of nervous response because it lacks a nervous

system. Protoplasm is itself a nervous system; the nerves of higher organisms are of protoplasm. The properties of tissues are the properties of the protoplasm of which they are made. The rhythmic pulsations of contractile tissues in higher organisms are but grosser manifestations of the innate rhythmic contractility of protoplasm wherever found.

### The Living and the Non-Living

Any statement on the distinction between the living and the non-living is obviously a daring speculation. But we may consider the question for a moment to see what a biochemist can do with it from a purely materialistic point of view.<sup>23</sup> It is evident from the immediately preceding pages that the proteins will form the basis of our speculation for, as already remarked, rarely has the central position of the proteins in the organization of protoplasm been questioned, for they alone display the specific properties of life. This does not imply that proteins alone are alive. Protoplasm is a heterogeneous system. It is alive only when a definite minimum of its constituents is present.

The uniqueness of living matter, that which distinguishes it from the non-living, may rest on chemical composition, or on structural features, on the way the amino acids are put together.

One may compare the situation to that of a clock which is made of a definite number of specific parts. Properly assembled these parts constitute a time-piece. If one part is missing, or one part but slightly out of alignment, the clock will not function; but with all parts in proper relationship to all others

the mechanism acquires a new function, namely, that of time keeping. Just so do the specific protoplasmic proteins, when structurally in proper relationship to each other acquire a new function, namely, life. Thus it may be that a definite coordination of parts results in an organized and harmonious whole raising protoplasm to a higher level in the scheme of things.

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# BIBLIOGRAPHY

<sup>1</sup> Abramson, H. A., L. S. Moyer and M. H. Gorin. Electrophoresis of Proteins, New York, 1942.

<sup>2</sup> Astbury, W. T. The X-ray study of proteins and related structures, Science Prog. No. 133, July 1939.

<sup>3</sup> Astbury, W. T. X-ray studies of the structure of compounds of biological interest, Ann. Rev. Biochem. 8: 113, 1939.

<sup>4</sup> X-ray studies of the molecular structure of myosin, Proc. Roy. Soc., London B, 129: 307, 1940.

<sup>5</sup> Banga, I. and A. Szent-Györgyi. Structure-Proteins, Science 92: 514, 1940.

<sup>6</sup> Beutner, R. and J. Lozner. The relation of life to electricity, Protoplasma 10: 1, 1930.

<sup>7</sup> Brooks, S. C. Studies on exosmosis, Am. Jour. Bot., 3: 483, 562, 1916.

<sup>8</sup> Dujardin, F. Sur les organismes inférieurs, Ann. Sci. Nat. 2e ser. Zool. 4: 343, 1835.

<sup>9</sup> Freundlich, H. Kapillarchemie, Leipzig, 1932.

<sup>10</sup> Harvey, E. N. Potential rhythms of the cerebral cortex during sleep, Science 81: 587, 1935.

<sup>11</sup> Kamiya, N. Control of protoplasmic streaming, Science 92: 462-463, 1940.

<sup>12</sup> Kamiya, N. Physical aspects of protoplasmic streaming, The Structure of Protoplasm, Mono., Ames, Iowa, 1942.

<sup>13</sup> Kiesel, A. Chemie des Protoplasmas, Protoplasma Mono. 4, Berlin, 1930.

<sup>14</sup> Landsteiner, K. Individual differences in human blood, Science 73: 403, 1931.

<sup>15</sup> Lewis, W. H. Arch. Exp. Zellforsch. 6: 253, 1928.

<sup>16</sup> Loeb, J. Proteins and the Theory of Colloidal Behavior, New York, 1922.

<sup>17</sup> Mark, H. Physical Chemistry of High Polymeric Systems, New York, 1940.

<sup>18</sup> Meyer, K. Protein and protoplasmic structure, The Structure of Protoplasm Mono., Ames, Iowa, 1942.

<sup>19</sup> Mohl, H. von. Über die Saftbewegung in Innern der Zellen. Bot. Ztg. 4: 73, 89, 1946.

<sup>20</sup> Moyer, L. Species relationships in Euphorbia as shown by the electrophoresis of latex, Am. J. Bot., 21: 293, 1934.

<sup>21</sup> Pauli, W. Colloid Chemistry of the Proteins, London, 1922.

<sup>22</sup> Pauling, L. The Nature of the Chemical Bond, Ithaca, N. Y., 1940.

<sup>23</sup> Pfeffer, W. Osmotische Untersuchungen, Leipzig, 1877.

<sup>24</sup> Scarth, G. The structural organization of plant protoplasm in the light of micrurgy, Protoplasma 2: 189-205, 1927.

<sup>27</sup> Seifriz, W. Protoplasm, New York, 1936.

<sup>31</sup> Seifriz, W. Protoplasmic streaming, Bot. Revs. (in press) 1943.

<sup>28</sup> Seifriz, W. A theory of protoplasmic streaming, Science 86: 397-398, 1937.

<sup>26</sup> Seifriz, W. The structure of protoplasm, Science 73: 648-649, 1931.

<sup>30</sup> Seifriz, W. A theory of anesthesia based on protoplasmic behavior, Anesthesiology 2: No. 3: 300-309, 1941.

<sup>25</sup> Seifriz, W. The physical properties of erythrocytes, Protoplasma 1: 345, 1926.

<sup>29</sup> Seifriz, W. A materialistic interpretation of life, Philosophy of Science 6: No. 3: 264, 1939.

<sup>32</sup> Sponsler, O. L. The molecule in biological studies as determined by X-rays. Quart. Rev. Biol., 8: 1, 1933.

<sup>33</sup> Sponsler, O. L. Molecular structure in protoplasm, The Structure of Protoplasm, Mono., Ames, Iowa, 1942.

<sup>34</sup> Taylor, C. V. Removal of the micronucleus in Euplotes, Anat. Rec. 25: 376, 1923.

## PROTOPLASMIC MODELS

See Protoplasm.

## PROTOTROPHIC

Capable of existence on inorganic matter.

**PROTOVERATRINE**

An alkaloid  $C_{32}H_{51}O_{11}N$ , from rhizome of *Veratrum album*; m.p., 245-250°; very toxic; benumbs the tongue.

**PROTOZOA**

Unicellular animals, e.g. amoeba, paramaecium.

**PROTOZOA, CLASSIFICATION**

A common classification is with reference to locomotor organs:

Class I—Rhizopoda; with pseudopodia ("root-foot").

Class II—Mastigophora; with flagella ("bear-whip").

Class III—Sporozoa; locomotor organs in adult stage ("seed-animal").

Class IV—Infusoria; with cilia ("poured in").

**PROTOZOOLOGY**

See Microbiology.

**PRULAURASIN**

dl-mandelonitrile-glucoside, m.p. 120-122°, a glycoside from the leaves of *Prunus laurocerasus*, having action similar to amygdalin.

**PRUNASE**

See Enzymes, Non-Proteolytic.

**PRUNITRIN**

Glucoside,  $C_{22}H_{24}O_{11} \cdot 4H_2O$ , from the bark of a species of *Prunus*.

**PRUNOL**

See Ursolic Acid.

**PRURIGO**

See Itching.

**PRUSSIAN BLUE**

$Fe_4 [Fe(CN)_6]_3$ ; ferric ferrocyanide used in making and grading ultrafilters.

**PSEUDOCONHYDRINE**

An alkaloid,  $C_8H_{17}ON$ , from seeds of *Conium maculatum*; m.p., 105°; said to be decidedly less toxic than coniine.

**PSEUDOEPHEDRINE**

An alkaloid; stereoisomer of ephedrine from leaves of *ephedra vulgaris*; m.p., 118-119°.

**PSEUDOGLOBULIN**

A globulin found in the blood serum. Unlike euglobulin it contains no phosphorus, is soluble in water and is precipitated by  $\frac{1}{2}$  saturated ammonium sulfate.

**PSEUDOHEMOGLOBIN**

See Verdohemoglobin.

**PSEUDOHYOSCYAMINE**

An alkaloid,  $C_{16}H_{32}O_1N$ ; has been suggested as sedative and hypnotic to control excitability.

**PSEUDOPELLETIERINE**

An alkaloid from bark of pomegranate tree; m.p., 48°; b.p., 246°; is a vasoconstrictor.

**PSEUDO-PEROXIDASES**

Enzymes, such as iron porphyrins, which catalyze the same kinds of reactions as peroxidase, but at a much lower rate; differ also by being thermostable.

**PSEUDOQUININE**

Isoquinine; an isomer of quinine melting at 190-191°; gives thalleoquin reaction like quinine and also exhibits fluorescence as does quinine in dil.  $H_2SO_4$ .

**PSEUDOSTROPHANTHIN**

A glucoside from seed of *Strophanthus Kombe*; is commonly called H-strophanthin and is said to be twice as powerful as K-strophanthin.

**PSEUDOYOHIMBINE**

An alkaloid,  $C_{21}H_{26}O_3N_2$ ; from bark of *Coryanthe Yohimbe* and melting at 264-265°.

**PSORIASIS**

A chronic skin disease of unknown cause showing as papules and

scales which are shed. Purine-low diets relieve symptoms, but the disease is incurable and is the stamping ground for any new remedy. Temporary results have been reported for sodium cacodylate, thyroxin, chrysarobin (an irritant), radiation (X-rays, sunlight, ultraviolet light).

# PSYCHIATRY, BIOCHEMISTRY IN RELATION TO

Recent reviews of the literature<sup>21, 23-25</sup> on biochemical investigations in psychiatry present a confusing array of conflicting reports which leave the reader with the impression that biochemical methods have contributed little to the understanding of mental disorders. Cameron<sup>7</sup> in the recent revision of his book, 'Objective and Experimental Psychiatry' has, however, made a beginning in relieving this confusion. It is the purpose of the present communication to demonstrate that biochemistry has already contributed a great deal to our understanding of mental disorders and to indicate the direction of present day investigations.

Biochemistry, the chemistry of living organism, is such a broad subject and has undergone such rapid development in so many fields that few people realize the extent of this science and its import for medicine and psychiatry.

In fact, every kind and degree of adjustment that a person makes in his daily life involves complex biochemical changes in his body. For example, social situations which produce fear or rage or other emotions constitute one of the most effective ways of bringing about biochemical changes in man and animals.<sup>9</sup> The recognition of the fact that mental activity influences

bodily processes in general has led many people to postulate that most diseases were "caused" by mental and emotional disorders. The great contributions of Pavlov, Freud, and Cannon have served to support such a conception; it should be emphasized however that these authorities themselves, being aware of the limitations of their work, made no such one-sided generalization.

Dramatic impetus has been given to an interest in the methods of physics and biochemistry by the extraordinary, if transient, relief of symptoms in mentally ill patients induced by insulin or metrazol, or electric shock. Unfortunately this interest tends to be as transient as the periods of symptomatic relief in the patients. The fact, however, that chemical and physical methods can produce these striking changes, should lead to a thorough exploration of biochemistry and physics in relation to mental processes in an effort to find more effective methods of treatment.

Of the numerous ramifications of biochemistry the development of our knowledge of energy exchange in man and animals may be chosen as an excellent example of the intimate relations between behavior and the chemistry of the body. Originally this process was conceived of as being relatively simple; food as calories when burned in the body produced an output of energy which could be measured in units of heat and of work. The elucidation of the steps involved in this energy exchange has opened whole new fields in chemistry and in medicine. Yet many gaps remain to be filled. Numerous contributions from these fields are important for psychiatry and will probably be even more important in the future.

The recognition of the importance of thyroid disorders in producing states of excitement or lethargy is one of the most brilliant contributions which may be cited. Not many years have elapsed since the time when patients with myxedema and hyperthyroidism could be found immured in mental hospitals along with the stuporous and excited states of unknown etiology. Although methods for the diagnosis and treatment of thyroid diseases have been remarkably advanced, much remains to be learned. Many patients in states of lethargy and with low basal metabolic rates do not respond to treatment with thyroid hormone<sup>8</sup> and presumably do not have thyroid deficiency. Again, many excited and agitated patients appear to have hyperthyroidism with basal metabolism rates above normal, yet removal of their thyroid glands does not relieve their symptoms. These patients are frequently mistreated because of the lack of methods for determining the amount of thyroid activity.

While it has long been known that iodine constituted a unique part of the thyroid hormone, the determination of blood serum iodine as an index to the amount of hormone has only recently been possible due to the technical difficulties of microchemistry. Man and Riggs,<sup>28, 33, 34</sup> have devised a practical method for determining the protein-bound iodine in serum and have shown that this fraction can be employed as a measure of the amount of active thyroid hormone. This method has proved effective in differentiating excited and depressed patients with hyperthyroidism from those with non thyroid disorders.<sup>32</sup>

In connection with the biochemistry of thyroid disorders it

should also be emphasized that these conditions are often precipitated by emotional conflicts. Consequently one has the opportunity to observe the interplay of constitutional predisposition, environmental difficulties, both psychological and dietary, and biochemical factors which enter into the process of making the person ill.

Only one aspect however, of the problem of energy exchanges in man is illuminated by the advances in biochemistry of the thyroid. Each endocrine organ produces one or more chemical substance; the hormones. The amount each gland secretes is controlled by the nervous system, which itself produces acetyl choline, and by the interaction of the hormones themselves. While it is known that animal drives and energy output are dependent on these delicate chemical intergrations,<sup>31</sup> our knowledge is too incomplete to make it possible to understand and control the behavior of the whole animal.

One of the most common complaints which physicians are asked to relieve is lack of energy. While it is well known that any disturbance of the delicately balanced chemical and physiological arrangements of the body, may produce varying degrees of diminution of energy output, a large proportion of these patients who lack energy do not appear to suffer from any of the known organic diseases. Many of these patients are eventually referred to a psychiatrist. As a considerable number of them are seriously incapacitated for months or years, no matter what psychotherapeutic methods may be employed, the psychiatrists have had ample opportunity to observe the course of their conditions.



We have learned that the ability or lack of ability to convert food into a large amount of work or play tends to be characteristic of certain families and that in members of such families high levels of activity may not be sustained but are interrupted by periods of inactivity. We have also observed that these cyclic disorders are more common in women and in people of stocky body-build. Such observations have led some psychiatrists to lay stress on genetic and constitutional factors as determining a person's potential energy and susceptibility to disorders in energy output.

In addition to these constitutional factors, many others take part in determining a person's potential capacity for work or play. Only a few can be mentioned here.

The brain must have a continual supply of oxygen, carbohydrates and enzymes.<sup>40</sup> Biochemical and physiological investigations,<sup>1, 12, 37</sup> have demonstrated that a few moments of oxygen and carbohydrate deprivation result in interruption of the nervous system activity. If the period of deprivation is prolonged more than these few moments death occurs; or if restoration occurs shortly before death, some cells of the brain may be destroyed, thereby permanently altering the person's potentialities for certain kinds of activity. This knowledge has led to a revision in the psychiatric interpretation of the significance of birth injuries and of the effects of carbon monoxide poisoning, of convulsive seizures and of other conditions which impair the oxygen supply to the brain. Particularly relevant is the work of the neurologists, showing that certain brain lesions may produce queer forms of

overactivity while others will result in underactivity.<sup>10</sup>

The successful correlation of physiological, electrophysical and chemical methods in the investigation of patients with epilepsy, by Lennox, Gibbs, Gibbs, and Nims,<sup>11, 29</sup> constitutes an important advance. They were thus able to demonstrate defects in the control of respiratory metabolism in epileptic patients which would have been overlooked by a one-sided approach.

The development of the field of carbohydrate metabolism has made it possible to recognize and treat previously mysterious states of weakness, fainting and convulsions due to low blood sugar. The effects of the pancreatic adenomas should be mentioned in this connection.<sup>38</sup> The demonstration of the sensitivity of the brain to lack of carbohydrate and Cannon's work on the effects of emotions have led psychiatrists all over the world to investigate carbohydrate metabolism in excited and depressed patients. As has so frequently happened in other fields of psychiatry, a great variety of conflicting discoveries have been reported. On the basis of recent work one can conclude that most of the apparently excited and overactive as well as depressed and underactive patients have normal amounts of sugar in their blood.<sup>4, 39</sup> This was considered contrary to Cannon's findings of emotional hyperglycemia in animals and of frequent glycosuria in students following examinations. Some of the psychiatrists, particularly Whitehorn and Bowman, were led to conclude that emotional hyperglycemia must be uncommon in man. Further studies, however, by Gildea, Mailhouse, and Morris<sup>14</sup> have demon-

strated that severe emotional reactions in normal people such as those produced by experiencing automobile accidents, by seeing a suicide, or by husbands' waiting for their wives to be delivered of babies, were commonly followed by hyperglycemia. It is probable therefore, that the abnormality in emotionally disturbed patients lies in their failure to mobilize sufficient sugar to raise the blood levels no matter how extreme their apparent emotional excitement may be.

Investigations of sugar tolerance curves have yielded conflicting results. It now appears however, that if allowance is made for the nutritional status, the nature of the diet, the disturbances in intestinal motility, (the latter can be ruled out by using the intravenous method)<sup>22</sup> the sugar tolerance curves in excited and depressed patients are rarely remarkable. The defect therefore probably lies in the nervous regulation of carbohydrate mobilization. In one group patients have low levels of blood sugar and spells of weakness unless frequently fed. In another group patients eat large amounts of food to relieve emotional tension, although they are frequently obese and become increasingly so with the passage of years. Diabetes mellitus not infrequently develops in this latter group.

Although the biochemists have established the importance of protein in determining the fundamental activities of biological organisms, little work has been done in the metabolism of proteins in patients with mental diseases. Gjessing's<sup>17</sup> meticulous studies of nitrogen balances in catatonic patients constitutes one of the few exceptions. His results suggest the presence of

a disturbance in protein chemistry in these patients but give no clue to its nature.

The recent developments in still another branch of biochemistry, i.e., the vitamin field,<sup>35</sup> have given us new insight into a certain small group of patients suffering from lethargy and hypochondriasis, for these symptoms may be due to partial deficiencies in B<sub>1</sub>, nicotinic acid, and other factors of the B complex.<sup>35</sup> It must, however, be stressed that most of the patients with depression of mood and energy do not respond to vitamin therapy.

On the other hand, the fact that B complex deficiencies can produce symptoms of depression indistinguishable from those of unknown etiology should lead us to look for other as yet unknown enzyme deficiencies in our patients.

Ever since Thudichum's brilliant and meticulous work, 1865-84, revealed that a considerable portion of nervous tissue was lipoid in nature there has been much speculation as to the role that lipoid substances must play in brain activity. More recently Bloor and co-workers<sup>2, 3</sup> and Brown,<sup>6</sup> have contributed evidence that tissue activity and even the activity of the whole animal are in some way dependent on the amount and character of the lipoids which they may contain. These observations have led to numerous investigations of lipoid metabolism in normal and mentally ill patients and particularly in those who suffer marked fluctuation in activity and also commonly have remarkable variations in body weight.<sup>13, 16, 26, 27</sup> These investigations may be summarized as follows: Normal people were found to have amounts of serum lipoids,

cholesterol, phospholipids, and fatty acids, which appear to be characteristic for each individual. Each individual undergoes rather wide fluctuations in lipoids in the course of a year but in spite of this retains his own level. Men with slender or leptosomic physique characteristically have low lipoids while those with stocky or pyknic physiques have high lipoids. In women the same relation appears to hold but is more difficult to demonstrate because of greater variation in fat deposits due to secondary effects of a different and more variable endocrine status. There is also some correspondence between high energy output and high lipoids, as well as the converse.

These findings proved of interest in connection with two groups of patients.<sup>18</sup> The patients in group I although endowed with a high energy output, suffer from marked fluctuations in this output. These patients tend to be stocky in physique and to have high lipoids; and they contrast strikingly with the second group who appear never to have had much energy and who are leptosomic in build. These two groups of patients have different sorts of mental symptoms. Group I, the manic depressive patients, have high lipoids, while the schizophrenic patients, Group II, have low lipoids. It is noteworthy that mixtures of these mental symptoms may occur in patients, in which cases the lipoids may or may not be high or low. These patients with manic depressive and schizophrenic disorders have been followed for five to ten years after the beginning of their illnesses in order to determine whether there was any relation between the level of serum lipoids and the outcome. The majority of the patients with high lipoids have

experienced apparently complete remissions, while those with low lipoids have had incomplete or no remissions.<sup>15</sup> These findings are necessarily empirical and the underlying biochemistry of these relations awaits clarification.

Some order may be introduced into this problem by utilizing a hypothesis introduced some years ago by Kahn.<sup>19</sup> According to this conception people are endowed with certain constitutional potentialities which determine their development as regards physique, temperament, capacity for growth, output of energy, resistance to disease, ability to recover from disease, etc. Some of these may be recognized at present, but others must await advances in the biochemistry of constitution, for further definition. For the present there appear to be pyknapophilic potentialities which are represented anatomically by pyknic body build, in terms of behavior by warmth of temperament, by high energy output, including sex drive, by strong resistance to disease, and by remarkable capacity for recovery if overwhelmed by disease. That high lipoids may well represent a biochemical measure of pyknapophilic potentialities is suggested by the studies just described where they were found in the pyknic people with high energy output and in the patients who proved to have a high capacity for recovery. Deficiency in these qualities may be considered the result of the predominance of leptophilic over pyknapophilic potentialities. The presence of leptophilic potentialities is indicated by leptosomic physique, cool temperament, low output of energy, weak sex drive, low resistance to disease, and poor capacity for recovery and restitution. In line with this evi-

dence low serum lipoids would constitute another evidence of leptophilic potentialities.

From what we know of body chemistry, the structure of cells and tissues depends primarily on the structural arrangements of protein molecules. There is evidence, however, that the lipoids, are in some way fitted into the intricacies of these patterns. Consequently, the amount and nature of lipoids in a tissue may well depend in part on these protein arrangements. Thus, the serum lipoids may reflect fundamental constitutional qualities because of their intimate ties with the structural protein.

From these considerations it would appear obvious that the next step in attempting to estimate pyknophilic potentialities in biochemical terms would lie in the direction of protein chemistry and particularly in stereo-chemistry and in stoichio-chemistry.

While the field of structural protein chemistry is advancing with all its implications, the biochemist in psychiatry is not allowed to forget the rapid development of endocrinology with the discovery of new hormones, many of which are apparently derived from cholesterol. Deficiencies in some part of the adrenal cortical hormones may account for some of the chronic states of weakness and depression in patients. At present, however, the available adrenal cortical substances appear to have little effect in these patients. The effects of new fractions, like Kendall's E substance,<sup>20</sup> should be investigated when such substances become available.

In discussing some of the ways of approaching the problem of

energy exchange it has been necessary to leave out reference to much of the work on the effects of environment on body chemistry, such as prolonged emotional stimuli and changes in weather, particularly heat, and cold.

The problems relating to the nervous control of body chemistry have also scarcely been touched upon.<sup>9</sup> The studies of Brobeck, Tepperman and Long<sup>5</sup> on the effects of hypothalamic lesions on appetite and, in turn, on the body weight of animals, have important implications for psychiatry where gross disturbances in appetite are common phenomena.

The examples chosen for discussion in this paper represent a few of the more concrete and simple contributions of biochemistry to psychiatry. Present-day biochemistry is actually in its infancy. Some of the cruder elements that make up the living animal have been discovered and roughly measured. But only a beginning has been made in the exploration of the delicate but extremely active and complex chemical systems that determine the functions of the living organism. This is particularly true of brain chemistry. An examination of Page's exhaustive review of Brain Chemistry in 1937<sup>30</sup> supports this point. There is also very little known of the chemistry of the degenerative diseases of the nervous system. Folling's discovery of phenylpyruvic acid in the urine of some mentally deficient patients has opened a new field of investigation. Jervis<sup>18</sup> has confirmed and extended this work. The developments of recent years have been so extraordinary and numerous that we can only guess at their implications for psychiatry.

The brilliant experiments of Schoenheimer<sup>38</sup> and his co-workers with isotopes of various kinds, including fatty acids and amino acids, have revealed continuous chemical changes to be taking place in the lipid and protein structures of the body that were formerly looked upon as relatively inert tissues. Yet in spite of this continual change, the structure as well as the steady state of the living organism persists. In the light of these observations chemical analysis of the blood at suitable intervals will yield more information with regard to body structure, i.e., constitution, than was formerly possible.

While these advances in chemistry of structure and integration in the living organism are occurring, many chemicals are being discovered or synthesized which are peculiarly effective in disturbing the organized forces of nature. At present the production of powerful enzymes and hormones appears to be out-stripping our knowledge of structure and function.

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#### REFERENCES

- <sup>1</sup> Barach, A. L., McFarland, R. A. and Seitz, C. P., The effects of oxygen deprivation on complex mental functions. *J. Aviat. Med.*, 1937, 8: 1.
- <sup>2</sup> Bloor, W. R., Fat transport in the animal body. *Physiol. Rev.*, 1939, 19: 557.
- <sup>3</sup> Bloor, W. R., Okey, R. and Corner, G. W., The relation of the lipids to physiological activity. *J. Biol. Chem.*, 1930, 86: 291.
- <sup>4</sup> Bowman, K. M. and Kassanin, J., Sugar content of the blood in emotional states. *Arch. Neurol. and Psychiat.*, 1929, 21: 342.
- <sup>5</sup> Brobeck, J. R., Tepperman, J. and Long, C. N. H., Further observations on experimental hypothalamic obesity. *Fed. Proc.*, Part II, *Fed. of Am. Soc. for Exper. Biol., Am. Physiol. Soc.*, 1942, 1: 10.
- <sup>6</sup> Brown, J. B., The nature of the highly unsaturated fatty acids stored in the lard from pigs fed on menhaden oil. *J. Biol. Chem.*, 1931, 90: 134.
- <sup>7</sup> Cameron, D. E., Objective and experimental psychiatry. 2nd ed. New York, Macmillan Company, 1941, 390 pp.
- <sup>8</sup> Cohen, L. H. and Fiermann, J. H., Metabolic cardiovascular and biochemical changes associated with experimentally induced hyperthyroidism in schizophrenia. *Endocrinol.*, 1938, 22: 548.
- <sup>9</sup> Dunbar, H. F., Emotions and bodily changes; a survey of the literature on psychosomatic inter-relationships, 1910-33. 2nd ed., with supplementary introduction and additional bibliography. New York, Columbia Univ. Press, 1938.
- <sup>10</sup> Fulton, J. F., Physiology of the nervous system. New York, Oxford Univ. Press, 1938.
- <sup>11</sup> Gibbs, E. L., Lennox, W. G., Nims, L. F. and Gibbs, F. A., Arterial and cerebral venous blood. *J. Biol. Chem.*, 1942, 144: 325.
- <sup>12</sup> Gildea, E. F. and Cobb, S., The effects of anemia on the cerebral cortex of the cat. *Arch. Neurol. and Psychiat.*, 1930, 23: 876.
- <sup>13</sup> Gildea, E. F., Kahn, E. and Man, E. B., The relationship between body build and serum lipoids and a discussion of these qualities as pyknicophilic and leptophilic factors in the structure of the personality. *Am. J. Psychiat.*, 1936, 92: 1247.
- <sup>14</sup> Gildea, E. F., Mailhouse, V. L. and Morris, D. P., The relationship between various emotional disturbances and the sugar content of the blood. *Am. J. Psychiat.*, 1935, 92: 115.
- <sup>15</sup> Gildea, E. F. and Man, E. B., Methods for estimating capacity for recovery in patients with manic depressive and schizophrenic psychoses. (In press) *Am. J. Psychiat.*, 1942.
- <sup>16</sup> Gildea, E. F., Man, E. B. and Biach, R. W., Serum protein, non-protein nitrogen and lipoids in schizophrenic and manic depressive psychoses. *Arch. Neurol. and Psychiat.*, 1940, 43: 932.
- <sup>17</sup> Gjessing, R., Disturbances of somatic function in catatonia with periodic course and their compensation. *J. Ment. Sci.*, 1938, 84: 608.
- <sup>18</sup> Jervis, G. A., Phenylpyruvic oligophrenia, introductory study of 50 cases of



- mental deficiency associated with excretion of phenylpyruvic acid. *Arch. Neurol. and Psychiat.*, 1937, 38: 944.
- <sup>19</sup> Kahn, E., Constitutional aspects of personality type. *Res. Publ. Ass. nerv. ment. Dis.*, Baltimore, Williams and Wilkins Co., 1933, 14: 138.
- <sup>20</sup> Kendall, E. C., The adrenal cortex. *Arch. Pathol.*, 1941, 32: 474.
- <sup>21</sup> Lewis, N. D., Research in dementia praecox. *The Nat'l Comm. for Mental Hygiene*. New York, 1936.
- <sup>22</sup> Lozner, E. L., Winkler, A. W. Taylor, F. H. L. and Peters, J. P., The intravenous glucose tolerance test. *J. Clin. Invest.*, 1941, 20: 507.
- <sup>23</sup> McFarland, R. A. and Goldstein, H., Biochemistry of the psychoneuroses. *Am. J. Psychiat.*, 1937, 93: 1073.
- <sup>24</sup> McFarland, R. A. and Goldstein, H., The biochemistry of dementia praecox. *Am. J. Psychiat.*, 1938, 95: 509.
- <sup>25</sup> McFarland, R. A. and Goldstein, H., The biochemistry of manic depressive psychoses. *Am. J. Psychiat.*, 1939, 96: 21.
- <sup>26</sup> Man, E. B. and Gildea, E. F., Serum lipoids in malnutrition. *J. Clin. Invest.*, 1936, 15: 203.
- <sup>27</sup> Man, E. B. and Gildea, E. F., Variations in lipemia of normal subjects. *J. Biol. Chem.*, 1937, 119: 769.
- <sup>28</sup> Man, E. B., Smirnow, A., Gildea, E. F. and Peters, J. P., Serum iodine fractions in hyperthyroidism. *J. Clin. Invest.*, 1942, 21: 773.
- <sup>29</sup> Nims, L. F., Gibbs, E. L., Lennox, W. G., Gibbs, F. A. and Williams, D., Adjustment of acid-base balance of patients with petit mal epilepsy to over-ventilation. *Arch. Neurol. and Psychiat.*, 1940, 43: 262.
- <sup>30</sup> Page, I. H., Chemistry of the brain. Springfield, Ill., C. C. Thomas, 1937.
- <sup>31</sup> Richter, C. P., Biology of drives. *Psychosom. Med.*, 1941, 3: 105.
- <sup>32</sup> Riggs, D. S., Gildea, E. F., Man, E. B. and Peters, J. P., Blood iodine in patients with thyroid disease. *J. Clin. Invest.*, 1941, 20: 345.
- <sup>33</sup> Riggs, D. S., Lavietes, P. H. and Man, E. B., Investigations of the nature of blood iodine. *J. Biol. Chem.*, 1942, 143: 363.
- <sup>34</sup> Riggs, D. S. and Man, E. B., A permanganate acid ashing micromethod for iodine determinations. I. Values in blood of normal subjects. *J. Biol. Chem.*, 1940, 134: 193.
- <sup>35</sup> The Role of nutritional deficiency in nervous and mental diseases. *Res. Publ. Ass. nerv. ment. Dis.*, New York, XXII, 1942. (In press.)
- <sup>36</sup> Schoenheimer, R., The dynamic state of body constituents. Cambridge, Mass., Harvard Univ. Press, 1942.
- <sup>37</sup> Weinberger, L. M., Gibbon, M. H. and Gibbon, J. H., Jr., Temporary arrest of the circulation to the central nervous system. *Arch. Neurol. and Psychiat.*, 1940, 43: 615 and 961.
- <sup>38</sup> White, B. V. and Gildea, E. F., Adenoma of the pancreas and hyperinsulinism. *New Eng. J. Med.*, 1937, 217: 307.
- <sup>39</sup> Whitehorn, J. C., The blood sugar in relation to emotional reactions. *Am. J. Psychiat.*, 1934, 13: 987.
- <sup>40</sup> Wortis, H., Some nutritional aspects of brain metabolism. *Psychiat. Quart.*, 1941, 15: 693.
- PSYCHOTRINE**  
An alkaloid,  $(\text{CH}_3\text{O})_3\text{C}_{25}\text{H}_{26}\text{N}_2$  OH, from root of *Cephaelis ipecacuanha*; m.p., 122°.
- PTERINES**  
Insect pigments formed by the condensation of 3 uric acid rings, e.g. leucopteryne (white), xanthopteryne (bright yellow).
- PTEROBILIN**  
The blue pigment of butterfly wings, an isomer of biliverdin.
- PTEROCARPIN**  
An amaroid,  $\text{C}_{16}\text{H}_{11}\text{O}_4(\text{OCH}_3)$ , from wood of *Pterocarpus santalinus*; m.p., 165°.
- PTOMAINES**  
A group of poisonous amines formed by bacterial decarboxylation of amino acids. See putrescine, cadaverine, muscarine. (Obs.)
- PTYALIN**  
A salivary amylase that can convert starch into dextrins, and ultimately to maltose; pH 6.0 and most active in presence of salt. See also Digestion.



**P.U.**

See Anterior Pituitary-like Principle.

**PUERPERAL CONVULSIONS**

See Eclampsia.

**PUKATEINE**

An alkaloid,  $C_{18}H_{17}O_8N$ , having no pronounced physiological action; m.p., 200°.

**PULEGONE**

A menthene, volatile oil from pennyroyal oil, b.p. 221°.

**PULSATION, CELLULAR**

See Protoplasm.

**PUNICINE**

See Pelletierine.

**PUPA**

Chrysalis; pro-nymph; stage of insect between larva and imago.

**PURDIE'S REAGENT**

A mixture of silver oxide and methyl iodide, used in methylating sugars.

**PURINE**

A heterocyclic organic compound which is not found free in nature but whose derivatives occur in very important groups of substances, as nucleic acids, caffeine, uric acid.

**PURINE BASE**

A base derived from purine, e.g. caffeine.

**v. PURJESZ TEST FOR BILIRUBIN IN URINE**

2-3 cc. of urine are shaken with 2 cc. 20% sulfosalicylic acid solution and 2-3 drops 30% hydrogen peroxide. On standing, a green color develops within a few minutes reaching a maximum in about ½ hour. A red color indicates a negative test.

Reference: Med. Klin. 33, 1271 (1937).

**PURPLE BACTERIA**

See Photosynthesis.

**PURPLE, VISUAL**

See Eye, Biochemistry of.

**PURPURA**

See Hemorrhagic Diatheses.

**PURPURIN**

Isopurpurine, Anthrapurpurine; 1,2,4-Trihydroxy-anthraquinone; m.p., 256-259° (anhydr.); occurs as glucoside in madder root; used as cotton dye, as stain in microscopy, and as calcium reagent.

**PURSHIANIN**

A glucoside from root Rhamnus purshiana melting at 237°.

**PUS TEST**

See Hirschfeld.

**PUTREFACTION**

See Microbiology.

**PUTRESCINE**

Tetramethylene diamine, m.p. 27-28°, found in putrefying tissues, probably formed from arginine by bacterial action; also found in ergot and in urine in cystinuria.

**PYELONEPHRITIS**

See Urology.

**PYGIDIUM**

See Abdomen.

**PYKNIC BODY BUILD**

See Psychiatry, Biochemistry of.

**PYKNOLEPSY**

See Epilepsy.

**PYLORUS**

See Gastro-Enterology.

**PYOCYANIN**

A blue, chloroform soluble pigment, produced by a group of bacteria now classified as *Ps. aeruginosa*, functioning as an oxidation-reduction system and having bactericidal properties; this pigment has now been synthe-

sized; m.p. 133°, nitrogen-linked cyclic compound,  $C_{26}H_{20}O_2N_4$ .

**PYORRHEA ALVEOLARIS**

Rigg's disease; a suppurative inflammation of the membrane lining the tooth sockets caused probably by bacterial infection and acid fermentation. An alkalizing diet may be indicated. Autogenous vaccines have been used in difficult cases. Potassium chlorate is the favored oxidizing agent for disinfection.

**PYRANOSE**

Referring to or having the pyran ring structure.

**PYRETHROSIN**

An amaroid,  $C_{34}H_{44}O_{10}$ , from flowers of *Chrysanthemum cinerariaefolium* melting at 188-189°.

**PYRETHRUM**

Dried root of *Anacyclus Pyrethrum*, used as an insecticide, delousing agent, rubefacient.

**PYREXIA**

High fever.

**PYRIDINOPROTEINS**

Consists of diphosphopyridinoproteins as enzymes requiring coenzyme I, and triphosphopyridinoproteins which require coenzyme II.

**PYRIDIUM**

Phenylazo- $\alpha$ ,  $\alpha$ -diaminopyridine monohydrochloride, brick-red; used internally in urogenital infections.

**PYRIDOXIN(E)**

Vitamin B<sub>6</sub>; the term replaces also the expressions adermin, rat antidermatitis vitamin, factor Y, factor 1, antiacrodynia factor, and vitamin H. It has been isolated and synthesized and has the structure of 2-methyl-2-hydroxy-4,5 di-(hydroxymethyl) pyridine.

Wheat germs, rice, fish liver and muscle are good sources and it is extremely wide spread in small quantities. Its deficiency is shown by a dermatitis, convulsions, microcytic hypochromic anemia and acceleration of hair graying. It is probably essential for hemoglobin formation, is "spared" by fat and will aggravate cortical necrosis of kidneys in rats on low choline. Its requirement is apparently proportional to metabolism and is higher in infectious fevers.

**PYRIDOXIN, ROLE IN PLANTS**

See Plant Growth Hormones.

**PYRIMIDINE**

An organic heterocyclic compound whose derivatives occur in such important compounds as the nucleic acids in the form of uracil, cytosine, and thymine; m.p. 20-22°; b.p. 123-124°.

**PYROCALCIFEROL**

An isomer of calciferol, m.p. 95°; obtained from it by thermal treatment. It has 4 rings and 3 conjugated double bonds.

**PYROPHOSPHATASE**

A phosphatase which degrades organic pyrophosphates to phosphates, e.g. in malt and in yeast. See Enzymes, Non-Proteolytic.

**PYRORACEMIC ACID**

See Pyruvic Acid.

**PYRROLE TESTS**

See Denigès, Montignie.

**PYRROLIDINE**

Tetrahydropyrrole; a saturated, 4 carbon 1 nitrogen heterocyclic compound; b.p., 87-89°; sp.gr., 0.852.

**PYRUVIC ACID**

$CH_3COCOOH$ ; a keto-fatty acid found in fermentation and as an

intermediate of metabolism, b.p. 90° C.

See Carbohydrate and Fat Catabolism.

**PYRUVIC ACID TESTS**

See Alvarez, Neuberg, Simon.

**PYRUVIC ALDEHYDE**

Methyl glyoxal; b.p. 72°; present in fermentations and is involved in breakdown of carbohydrates.

**PYRUVIC OXIDASE  
(ANIMAL TISSUE)**

A thiaminoprotein enzyme of the

avitaminous brain which catalyzes the aerobic oxidation of pyruvic acid to acetic acid and CO<sub>2</sub> or the anaerobic dismutation of pyruvic acid to CO<sub>2</sub>, acetic and lactic acids; requires Mg or Mn.

**PYRUVIC OXIDASE  
(BACTERIA)**

A thiaminoprotein enzyme of Bact. *Delbruckii* which promotes an oxidative decarboxylation in which acetic acid is formed; similar products are derived from *Gonococcus* and *Staphylococcus*.

## Q

### QO<sub>2</sub>

The cubic millimeters of oxygen consumed by an organism or per 100 million organisms (protozoa) at NTP (normal temperature and pressure) per hour; instead of per organism, sometimes per milligram dry tissue.

### QUASSIA

Bitterwood; bitterash; wood of *Picrena excelsa*, a tree of Jamaica, contains "quassin," a bitter principle used in tonics and as a stomachic, also against pinworms.

### QUASTEL REACTION FOR o-DIHYDROXYPHENOLS

o-Dihydroxyphenols give a reddish-brown color when an aqueous solution is treated with 0.5 cc. acetic acid and 1 cc. 14% ammonium molybdate solution.

Reference: Zeit. anal. Chem. 94, 370 (1933).

### QUEBRACHAMINE

$C_{16}H_{26}N_2$ ; m.p. 145-147°; from bark of *apidosperma quebracho-blanco*, Schlecht., Apocynaceae; paralyzes respiration.

### QUEBRACHINE

See Yohimbine.

### QUEBRACHITOL

Methyl ether of l-inositol, found in quebracho bark and rubber latex.

### QUERCETAGETIN

An amaroid,  $C_{15}H_{10}O_8$ , from flowers of African marigold; m.p., 318-320°.

### QUERCETIN

$C_{15}H_{10}O_7 \cdot H_2O$ , present in the rind of many fruits; m.p. 312-314°.

### QUERCETIN-RHAMNOSIDE

See Quercitrin.

### QUERCIMELIN

See Quercitrin.

### QUERCIMERITRIN

A chromo-glucoside,  $C_{21}H_{20}O_{12}$ ; a compound of glucose and quercetin occurring in certain flowers; m.p. 247-249°.

See Flavonol Glycosides.

### QUERCIN

See Scyllitol.

### QUERCITOL

Acorn sugar; m.p. 234-235° (d-form); isomers of inositols (10); d-quercitol occurs in acorns and palm leaves.

### QUERCITRIN

$C_{21}H_{22}O_{12} \cdot 2H_2O$ ; quercimelin; quercitrinic acid; a glucoside of the bark of oak consisting of rhamnose and quercetin. Bright yellow needles or plates, m.p. anhydrous form 168°.

### QUERCITRINIC ACID

See Quercitrin.

# QUICK'S TEST

A test of liver detoxicating function by the administration of sodium benzoate and determination of hippuric acid in the urine.

# QUINHYDRONE ELECTRODE

An electrode containing an equimolecular mixture of quinone and hydroquinone. It is an oxidation-reduction system, the developed potential of which varies with the hydrogen ion concentration of the solution. It is therefore used to measure hydrogen ion concentration. It gives accurate results only when there is no other oxidation-reduction potential in the system.

# QUINIC ACID

Chinic acid, kinic acid; m.p., 162-163°; carboxylic acid of tetrahydroxycyclohexane, found in cinchona, coffee, etc.

# QUINICINE

Chinicine; quinotoxine; m.p. about 60°; an isomer of quinine found in small amounts in cinchona bark; more toxic than quinine.

# QUINIDINE

Conquinine;  $\beta$ -quinine; pitayine;  $C_{20}H_{24}O_2N_2$ ; dextrarotary isomer of quinine, found in cinchona to the extent of 0.25-1.5%, resembles quinine in action; m.p. 170-171°.

# QUININE

$C_{20}H_{24}O_2N_2$ ,  $3H_2O$ , m.p. anhydrous form, 175°; alkaloid of cinchona bark, a specific for malaria, also a tonic and cold cure; retards protoplasmic activity including fermentation and action of some enzymes like pepsin and trypsin.

# $\beta$ -QUININE

See Quinidine.

# QUININE TEST

See Giemsa.

# QUINOIDINE

A mixture of alkaloids of cinchona, other than quinine, quinidine, cinchonine and cinchonidine, obtained from the mother liquors of quinine manufacture; has a milder effect than quinine.

# QUINOTOXINE

See Quinicine.

## R

### RACEMIC MIXTURE OR COMPOUND

A mixture of equal amounts of dextro (d-) and levo (l-) rotatory isomers, with a resultant optical activity of zero.

### RACHITIS

See Rickets.

### RACEMIC ACID

See Tartaric Acid (or dl-tartaric acid).

### RADIATION, BIOLOGICAL EFFECTS OF

The term radiation includes energy in the form of the  $\gamma$  rays of radium, X-rays, ultraviolet radiation, visible light, infra-red radiation or heat, and electric or radio-waves. The shorter the wavelength the more energy is contained in a quantum or unit of radiation. Quanta of radio-waves and infra-red radiation do not contain enough energy to affect ordinary chemical reactions. X-rays and  $\gamma$  rays contain enough energy to completely ionize molecules, but they are so penetrating that only a small portion of the incident energy is absorbed in an ordinary reaction system. Ultraviolet radiation is readily absorbed and is consequently very effective in bringing about chemical

reactions. The absorption of radiation in the ultraviolet and to a lesser extent in the visible region results in the displacement of electrons in the absorbing molecules and these activated molecules are then capable of entering into photochemical reactions.

**Primary and Secondary Light Reactions:** In a primary light reaction a substance A is changed to form B on absorption of radiation. If B is stable the amount formed is proportional to the energy absorbed. Usually B is unstable and may be represented only by the condition of activation in the absorbing molecule. B may revert to A with production of fluorescence. Or B may react with other substances present (i.e.  $B + C \rightarrow D$ ). In that case the amount of the end product D formed is not proportional to the amount of energy absorbed. The fact that most of the photochemical reactions which are concerned in the biological effects of radiation are secondary reactions accounts for their failure to obey the Einstein Photochemical Equivalence Law which properly pertains only to the primary process.

Absorbed radiation, particularly



in the short wave region, may initiate photochemical reactions of many types in gases, solids and liquids. These have been extensively studied.<sup>1</sup> Those which concern us in considering the biological effects of radiation are the reactions produced by the absorption of radiation in the organic constituents of living cells. We may, therefore, consider first what is known in regard to the effect of radiation on proteins and sterols *in vitro* and secondly the effect produced on the living organism when these substances absorb radiation in the living cell.

#### Effect of Radiation on Organic Substances

##### Proteins, Amino-acids and Related Substances:

Proteins begin to absorb at approximately 310 m $\mu$ . The absorption increases to a maximum at 280 m $\mu$ , falls to a minimum at 250 m $\mu$  and then rises again for shorter wavelengths. Wavelengths longer than approximately 310 m $\mu$  produce no effect on proteins, but those shorter than 310 m $\mu$ , which are present in variable amounts in sunlight, and to a much greater degree in carbon and metallic arcs and mercury vapor arcs, produce marked changes.

Recent work on the molecular weight of proteins has shown that they have a very large molecular weight and are very subject to dissociation or association with change of pH or on the addition of salts or other proteins.<sup>2</sup> Proteins may exist in long-chain or globular form and are subject to change of configuration. On absorption of ultraviolet radiation active labile protein molecules are denatured and are no longer capable of forming part of a living cell. The exact nature

of this denaturation change is still unknown.

A denatured protein is more easily precipitated than a native protein and denaturation may be thought of as a change in the configuration of the native protein resulting in a loss of solubility. Proteins are irreversibly denatured on exposure to ultraviolet radiation at any pH and at any temperature, but this denaturation is not necessarily followed by coagulation.<sup>3</sup> The primary process, or light denaturation, is a unimolecular reaction with a temperature coefficient of 1. This primary process may be followed by secondary changes leading to coagulation. The second step is a reaction between the light-denatured molecule and water similar to heat-denaturation but occurring at a lower temperature, with a high temperature coefficient. The final step is the flocculation of the light and heat denatured molecules which takes place only near the isoelectric point in salt-free proteins, but over a wider pH range in the presence of certain salts.

Proteins are similarly denatured on exposure to X-rays and  $\gamma$  rays but as these radiations are so little absorbed by protein solutions it requires days of radiation to produce a measurable result.

Proteins after light-denaturation show a marked increase in absorption in the ultraviolet region.<sup>4</sup>

In addition to the radiation change we call denaturation, proteins may be photo-oxidized with the formation of protein derivatives (proteoses).<sup>5</sup> Denaturation and molecular splitting are due to different processes as the latter change requires oxygen and the former is independent of it.

Sulfhydryl groups that are not present in the native state appear when a protein is denatured by radiation.<sup>6,7</sup> The presence of these groups would promote oxidations and reductions in radiated tissues.

**Amino-acids:** Many studies have been made of the effect of radiation on individual amino-acids. Melanin is believed to be the end product of the oxidation of tyrosin by ultraviolet radiation in the presence of an oxidase present in the skin cells.<sup>8</sup>

It can be demonstrated that histamine can be produced by the irradiation of histidine at pH 12 in the absence of oxygen<sup>9</sup> but the occurrence of this change in irradiated skin tissue is uncertain.<sup>10</sup>

**Enzymes and Hormones:** Since the activity of an enzyme depends upon the integrity of its colloidal protein component, the destruction of the activity of enzymes by ultraviolet radiation is intimately bound up with the effects of radiation on proteins. This subject has been studied extensively and the specific conditions of wavelength of radiation, pH of solution, and other factors determining the effect on individual enzymes are given in Ellis and Wells.<sup>1</sup>

In the same book there is a concise account of the effect of radiation on hormones and on the substances concerned in immunological reactions. In general one may state that they are all inactivated by ultraviolet radiation on exposure *in vitro*.

**Sterols:** Ergosterol, on exposure to ultraviolet radiation, goes through a series of isomeric changes and one of these radiation products is calciferol or vitamin D.<sup>11</sup> Purified cholesterol does not produce vitamin D on radiation, but ordinary

cholesterol, as found in the tissues, can be so activated. Despite early evidence that ergosterol is the provitamin in cholesterol later experiments indicated that such is not the case.<sup>12</sup> In all probability 7-dehydrocholesterol is the significant provitamin in the skin.<sup>13</sup> Absorption spectra of 7-dehydrocholesterol and ergosterol are similar and show specific changes on radiation.

The structural similarity between carcinogenic hydrocarbons and sterols has suggested to some investigators that carcinogens may be formed from sterols in the skin by radiation.<sup>14</sup> Experimental work has failed to substantiate this hypothesis.<sup>15</sup>

#### Effect of Radiation on the Living Cell

**Bacteria and Protozoa:** Radiation shorter than 310 mμ, which is absorbed by proteins and sterols, is highly destructive to all living cells. Consequently ultraviolet radiation has a marked lethal effect on bacteria and protozoa which has been extensively studied. The sensitivity curve of bacteria to radiation<sup>16</sup> is so similar to the absorption curve of proteins that there seems little doubt that the lethal action on small organisms is linked with the denaturation of their protein constituents. Viruses have been found to be far more resistant to radiation than bacteria.<sup>17</sup>

The lethal effect of X-rays and γ rays on cells has been summarized in recent reviews.<sup>18, 19</sup> Different types of cells vary greatly in their sensitivity.

Recent advances in nuclear physics have focussed the interest of many investigators on the biological effect produced by neutrons and the comparative effect of neu-

trons and X-rays. Neutrons, like X-rays and the  $\alpha$ ,  $\beta$  and  $\gamma$  rays of radium produce biological effects because of the ionization they cause. Neutrons on collision give up their energy to hydrogen nuclei and produce intense ionization over a short path. They are, therefore, more effective biologically than X-rays and  $\gamma$  rays which cause a small degree of ionization over a long path.<sup>20, 21</sup>

**Large Organisms:** Ultraviolet radiation is not lethal to larger organisms because it is absorbed in such a very thin layer of the body surface. The direct effect therefore is on the eyes and skin only. Certain important indirect effects are produced by diffusion of the products of light injury in the skin.

**Eye:** The absorption of the cornea begins at 300  $m\mu$  so that if radiation shorter than 300  $m\mu$  falls on the eye it is absorbed by the cornea and conjunctiva and produces a severe inflammation. The aqueous humor absorbs no radiation longer than 250  $m\mu$  and the absorption of the vitreous humor is similar to that of the cornea. Therefore, the cornea screens the aqueous and vitreous from any effect. The absorption of the lens varies somewhat in different animals and increases with age. The limit of transmission varies from 313  $m\mu$  in infants to 400  $m\mu$  in elderly people, the average being 336  $m\mu$ . Therefore, certain ultraviolet wavelengths between 300 and 336  $m\mu$  penetrate the cornea, are absorbed by the lens, and denature the lens proteins. At the pH of the lens the denatured protein does not precipitate unless the salt content of the lens increases above normal but a combination of radiation and increased

salt content may account for senile cataract.<sup>22, 23</sup>

Wavelengths from 400 to 760  $m\mu$ , which we call visible light, penetrate to the retina, are absorbed there, and produce the photochemical changes which give rise to visual sensations.

Wavelengths longer than 760  $m\mu$  are absorbed throughout the eye and are transformed into heat. Exposure of the eye to intense sources of infrared radiation, as in exposure to molten glass or metal, may produce cataract, probably by disturbing the nutrition of the lens.

Eclipse blindness is a scotoma due to heat necrosis of the retina. This is caused largely by infrared radiation but intense visible radiation may be a contributing factor. Snowblindness is caused by reflection of intense sunlight into the eye by snowfields or water and sometimes by sand. The reflected ultraviolet radiation produces a conjunctivitis and the reflected visible and infra-red radiation may produce temporary scotomata.

**Skin, Direct Effects:** It may be stated in general that living skin 0.1 mm thick absorbs all ultraviolet radiation shorter than 290  $m\mu$  and skin 1.0 mm thick absorbs rays shorter than 365  $m\mu$ . It should be remembered however that the intensity reaching a certain depth  $d$  beneath the surface ( $I_d$ ) depends upon the intensity at the surface  $I_0$ , as  $I_d = I_0 e^{-md}$ , where  $m$  is the absorption coefficient for the wavelength in question. So, although the stratum corneum may absorb all the incident ultraviolet radiation shorter than 290  $m\mu$ , and reduce radiation of 300  $m\mu$  to one-half, still, if the incident radiation is very intense, an appreciable

amount may reach the dermis.<sup>24</sup>

Visible and infra-red radiation penetrate further having maximum transmission at 1150 mμ. Unless the skin is sensitized the chief result is a rise in temperature.

Ultraviolet radiation shorter than 315 mμ produces the familiar inflammatory reaction known as sunburn. After a latent period, which varies in length with the intensity of radiation and the temperature of the skin, there is an erythema due to capillary dilatation, followed by pigmentation and peeling. The effect begins at 315 mμ, and the sensitivity increases to a sharp maximum at 297 mμ, falls to a minimum at 280 mμ and then increases towards shorter wavelengths.<sup>25, 26, 27</sup> The erythema at first has a sharp outline but later becomes diffuse with radiating streaks. Lewis<sup>28</sup> has, therefore, suggested that it is due to the release of an H-colloid from the damaged cells with a histamine-like action. Ellinger has suggested that this may in fact be histamine<sup>10</sup> but the length of the latent period suggests a macromolecule with a slow diffusion rate. Mitchell<sup>29</sup> gives evidence for believing that the H-colloid is a proteose formed by photolysis of proteins. By assuming that the stratum corneum acts as a screen or filter, and that the photolysis occurs in the stratum mucosum, he calculates the wavelength effectiveness at this depth for protein constituents and finds that it agrees well with the experimental sensitivity curve of the skin.

It has long been known that though X-rays and γ rays destroy cancer cells they may stimulate the formation of cancer in normal tissue. More recently it has been shown that excessive exposure to ultraviolet radiation results in the

production of skin cancer.<sup>30, 31</sup> The wavelength sensitivity curve of the skin for this effect is the same as for skin erythema. The close structural similarity between carcinogenic hydrocarbons and sterols suggests, however, that skin cancer is associated with changes produced by radiation in skin sterols rather than in proteins. Roffo links the effect with an increase in the cholesterol content of the skin after radiation.<sup>14</sup> It has been suggested that radiated cholesterol may become carcinogenic but direct proof of this is lacking.<sup>15</sup>

X-rays and the γ rays of radium penetrate deeply into the body, ionize cellular constituents and produce injury where absorbed. This injury may be lethal or sublethal leading to degenerative changes such as faulty mitosis. A comprehensive summary of the effect of these radiations on organs and body systems is given by Warren.<sup>32</sup>

**Skin, Indirect Effects:** Though the direct effects of radiation are destructive some of the by-products of injury may be beneficial to the body. The activation of provitamin D in the skin results in the cure and prevention of rickets, through the effect of vitamin D on calcium and phosphorus metabolism.

The absorption of the products of tissue damage into the circulation apparently produces other less well defined results as after exposure to ultraviolet radiation the blood sugar is lowered, there is stimulation of the thyroid and an increased formation and excretion of androsterones.<sup>33</sup> Temporary effects are produced on blood volume, blood pressure and the number and distribution of blood cells. Cells injured by radiation produce a sub-

stance or substances which stimulate growth.<sup>34</sup>

**Sensitization to Visible Light:** Ordinarily visible light has no effect other than to raise the skin temperature and increase peripheral circulation. It has, however, been shown<sup>35</sup> that the third generation of rats raised in visible light show increased growth compared with those raised in the dark.

However, if body tissues are sensitized to visible radiation extensive effects are produced. A sensitized reaction is one in which there is a photocatalyst present which may itself be unaffected by the radiation. The way in which the catalyst functions may vary. In some cases it forms a loose compound with the reactants and this compound is excited by light in the absorption band of the catalyst or sensitizer. In other cases the catalyst is excited by absorbed radiation and transmits its energy to a reacting molecule by collision. Many photochemical reactions, which are ordinarily initiated by ultraviolet radiation only, proceed in visible light in the presence of a sensitizer. It has been found possible to sensitize bacteria, protozoa, red blood cells and enzymes to the action of visible light. The changes produced in biological materials by visible light plus a sensitizer differ from those produced by ultraviolet radiation in that the former require oxygen whereas this is not necessarily true of the latter.<sup>36</sup>

Many substances act as sensitizers *in vitro* but only eosin, chlorophyll and certain derivatives of hemoglobin are effective *in vivo*. Hematoporphyrin is the most potent of these sensitizers. Animals injected with small amounts of this

substance are healthy in the dark but die in the light and remain sensitized a long time as the hematoporphyrin forms a stable photosensitive compound with some element of the skin tissue. Death in these sensitized animals is due to fall in blood pressure.<sup>37</sup> As visible light penetrates further than ultraviolet radiation the depth of tissue damage and the extent of capillary dilatation is much greater. Exposure of a large sensitized area with extensive capillary dilatation brings about a fall in blood pressure and death.

Light dermatoses occur in animals following the ingestion of certain plants. The most familiar are buckwheat poisoning, hypericium (St. Johnswort poisoning) and geeldikkop.<sup>38</sup> Sheard<sup>38</sup> and Chick<sup>39</sup> have been able to produce buckwheat poisoning in experimental animals by means of fresh green buckwheat, flowers, or husks of seeds.

Apparently the body often contains potential sensitizers from derivatives of hemoglobin and chlorophyll but has a mechanism that ordinarily prevents them from reaching the skin in sensitizing form. Digestive processes in the case of ingested material and metabolic processes in the case of hemoglobin formation results in a destruction of sensitizing characteristics. When dietary disturbances are severe enough to interfere with these processes spontaneous light sensitization may occur.

Certain carcinogenic agents have been found to sensitize the skin and protozoa to visible light.<sup>40</sup> One would expect this to favor cancer formation on exposure to visible light but two groups of observers have found that visible light, coin-



cident with painting by benzpyrene, inhibits the production of tumors in the skin of mice.<sup>41, 42, 43</sup>

**Botanical Effects:** No mention has been made of the extensive researches on the effect of visible and ultraviolet radiation on plant growth. Reviews on radiation and plant physiology may be found in Duggar's, "Biological Effects of Radiation."

**Genetics:** Radiation has been a most valuable tool in the study of mutations. X-rays and  $\gamma$  rays of sublethal intensity increase the rate at which mutations occur in both animals and plants.

**Conclusion:** Ultraviolet radiation, when absorbed, is destructive to living cells due to the denaturation of the cell proteins and the changes produced in cell sterols and lipoids. This produces lethal effects in small organisms and viruses, loss of the characteristic properties of substances such as proteins, enzymes and hormones, local inflammation in the skin of larger animals and indirect effects from the products of tissue damage. Visible radiation has similar effects only in the presence of a sensitizer. X-rays and  $\gamma$  rays are also destructive to cells, but because of their penetrating power the effects are not localized in the skin but are distributed throughout the organism.

JANET HOWELL CLARK,  
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#### REFERENCES

<sup>1</sup> Ellis, C. and Wells, A. A. (revised by F. F. Heyroth), "The Chemical Action of Ultraviolet Rays," Reinhold Publishing Corp. (1941).

<sup>2</sup> Svedberg, T., Chem. Rev., 20: 81 (1937).

<sup>3</sup> Clark, J. H., J. Gen. Physiol., 19: 199 (1935).

<sup>4</sup> Spiegel-Adolf, M., Arch. Path., 12: 533 (1931).

<sup>5</sup> Bernhart, F. W., J. Biol. Chem., 128: 289 (1939).

<sup>6</sup> Wels, P. and Jokisch, M., Strahlenther., 58: 1 (1937).

<sup>7</sup> Mirsky, A. E. and Anson, M. J., J. Gen. Physiol., 19: 427 (1936).

<sup>8</sup> Arnow, L. E., J. Biol. Chem., 120: 151 (1937).

<sup>9</sup> Holtz, P., Arch. fur Exp. Path. & Pharmacol., 175: 97 (1934).

<sup>10</sup> Ellinger, F., Arch. f. Exp. Path. & Pharmacol., 153: 120 (1930).

<sup>11</sup> Bills, C. E., p. 323, Duggar, "Biological Effects of Radiation," McGraw Hill (1936).

<sup>12</sup> Waddell, J., J. Biol. Chem., 105: 711 (1934).

<sup>13</sup> Bunker, J. W. M., Harris, R. S. and Mosher, L. M., J. Amer. Chem. Soc., 62: 508, 1760 (1940).

<sup>14</sup> Roffo, A. H., Amer. J. Cancer, 17: 42 (1933).

<sup>15</sup> Bergman, W., Stavely, H. E., Strong, L. C. and Smith, G. M., Amer. J. Cancer, 38: 81 (1940).

<sup>16</sup> Gates, F. L., J. Gen. Physiol., 13: 231, 249 (1929).

<sup>17</sup> Dugger, B. M. and Hollaender, A., J. Bact., 27: 219, 241 (1934).

<sup>18</sup> Scott, C. M., Med. Res. Council Spec. Rep. Ser. No. 223 (1937).

<sup>19</sup> Crowther, J. A., Brit. J. Radiol., 11: 132 (1938).

<sup>20</sup> Zirkle, R. E., Aebersold, P. C. and Dempster, E. R., Amer. J. Cancer, 29: 556 (1937).

<sup>21</sup> Lawrence, E. O., Radiology, 29: 313 (1937).

<sup>22</sup> Burge, W. E., Amer. J. Physiol., 39: 335 (1915-16).

<sup>23</sup> Clark, J. H., Amer. J. Physiol., 111: 538 (1935).

<sup>24</sup> Miescher, G., Strahlenther., 35: 403 (1930).

<sup>25</sup> Hausser, K. W. and Vahle, W., Strahlenther., 13: 41 (1922).

<sup>26</sup> Luckiesh, M., Holladay, L. L. and Taylor, A. H., J. Opt. Soc. Amer., 20: 423 (1930).

<sup>27</sup> Coblenz, W. W., Stair, R. and Hogue, J. M., Bur. Stand. Res., Paper No. 433 (1932).

<sup>28</sup> Lewis, Sir Thomas, "Blood Vessels of the Human Skin and their Responses," London, Shaw & Sons (1927).



<sup>29</sup> Mitchell, J. S., Proc. Roy. Soc. B, 126: 241 (1938).

<sup>30</sup> Findley, G. M., Lancet, 2: 1070(1928).

<sup>31</sup> Roffo, A. H., Z. Krebsforsch., 41: 448 (1935).

<sup>32</sup> Warren, S. L., p. 473, Duggar, "Biological Effects of Radiation," McGraw Hill (1936).

<sup>33</sup> Laurens, H., Am. Rev. Physiol., 3: 21 (1941).

<sup>34</sup> Sperti, G. S., Studies Inst. Divi Thomae, Vol. 3: 17 (1941).

<sup>35</sup> Luce-Clausen, E. M. and Brown, E. F., J. Nutrition, 18: 537, 551 (1939).

<sup>36</sup> Blum, H. F., "Photodynamic Action and Diseases Caused by Light," Reinhold Pub. Corp. (1941).

<sup>37</sup> Rask, E. N. and Howell, W. H., Amer. J. Physiol., 84: 363 (1928).

<sup>38</sup> Sheard, C. Caylor, H. D. & Schlottbauer, C. F., J. Exp. Med., 47: 1013(1928).

<sup>39</sup> Chick, H., J. of Physiol., 100: 212 (1941).

<sup>40</sup> Doniach, I. and Mottram, J. C., Nature, 140: 588, 933 (1937).

<sup>41</sup> Doniach, I. and Mottram, J. C., Amer. J. Cancer, 39: 234 (1940).

<sup>42</sup> Morton, J. J., Luce-Clausen, E. M. and Mahoney, E. B., Amer. J. Roentg., 43: 896 (1940).

<sup>43</sup> Morton, J. J., Luce-Clausen, E. M. and Mahoney, E. B., Cancer Res., 2: 256 (1942).

See also NEUTRONS, BIOLOGICAL EFFECTS OF.

## RADIOPAQUE

Opaque to the Roentgen ray; not permitting the passage of radiant energy.

## RAFFINASE

See Enzymes, Non-Proteolytic.

## RAFFINOSE

A non-reducing tri-saccharide found in beet sugar. Not a useful supply of energy for man. It is 2- $\beta$ -fructofuranose-1- $\alpha$ -glucose-6- $\alpha$ -galactoside. Also found in cotton seed meal (8%) and molasses, m.p. 118°. See Trisaccharides.

## RANWEZ REACTION FOR PHENOBARBITAL

0.1 gm. phenobarbital is heated with 0.5 gm. potassium nitrate and 2 cc. sulfuric acid for 10 minutes; the nitrophenobarbital is reduced to aminophenobarbital with zinc. The addition of 0.1 gm. sodium nitrite and a sodium hydroxide solution of  $\beta$ -naphthol gives a blood-red color.

Reference: J. pharm. Belg. 6, 410 (1924).

## RAPIC ACID

An isomer of oleic acid, found in rape oil, the position of the double bond being unknown.

## RASPAIL REACTION FOR LECITHIN

A solution of lecithin in concentrated sulfuric acid gives a yellow color changing to purple-red on the addition of sugar.

Reference: Synthesis of Lecithins, Diss. Zurich 1911.

## RAT ANTIDERMATITIS VITAMIN

See Pyridoxine.

## RAYBIN REACTION FOR SUCROSE

A solution of 40-50 mg. of sugar in 5 cc. of 7% sodium hydroxide solution is shaken with 7-10 mg. diazouracil until dissolved, the solution being kept cold; a blue-green color forms. Addition of a magnesium salt produces a stable precipitate.

Reference: J. A. C. S. 55, 2603 (1933).

## REAGIN

See Immunological Phenomena.

## RECAPTURE SYNTHESIS

See Carbohydrate and Fat Catabolism.

**RECEPTORS**

See Nervous System.

**REDOX**

The phenomenon of mutual reduction and oxidation; oxidation-reduction (abbr.).

**REDUCASE**

An obsolescent term for a dehydrogenase.

**REDUCTASE**

An obsolescent term for a dehydrogenase.

**REDUCTION**

The gain, by the substance being reduced, of one or more electrons. Invariably accompanied by oxidation of some other member of the system under consideration.

The term covers also the addition of hydrogen atoms and the loss of oxygen atoms.

**REFLEX ARC**

See Nervous System.

**REFLEXES**

See Nervous System.

**REGENERATION, EPITHELIAL**

See Wound Healing.

**REICHARD REACTIONS FOR NICOTINE AND CONIINE**

On addition of a drop of nicotine and a drop of hydrochloric acid to dry, finely powdered copper oxychloride, a violet-blue mass is obtained; coniine gives a bright green solution gradually becoming colorless when treated in the same way.

Nicotine turns yellow when its solution with  $\alpha$ -naphthol is treated with hydrochloric acid; coniine remains colorless. The addition of hydrochloric acid to a mixture of nicotine and bismuth subnitrate gives an intense yellow color; coniine remains white.

Reference: Pharm. Zentralhalle 46, 309 (1905).

**REICHERT-MEISSL NUMBER**

A test usually applied to esterified fatty acids to determine the relative amounts of high and low molecular weight acids. It is defined as the number of cc. of 0.1N KOH required to neutralize the steam distillate of 5 grams of saponified fat (low mol. wt. fatty acids.)

**REINECKE'S SALT**

$[\text{Cr}(\text{CNS})_4(\text{NH}_3)_2]\text{NH}_4\cdot\text{H}_2\text{O}$ ; forms very insoluble compounds with secondary and tertiary amines. Used to precipitate proline and oxyproline from protein hydrolysates. (The K salt is also known by this name.)

Reference: Zeit. anal. Chem. 69, 114 (1926).

**RENAL DIABETES**

See Glycosurias, Non-Diabetic.

**RENAL GLYCOSURIA**

See Glycosurias, Non-Diabetic.

**RENAL HYPERTENSION**

See Oxyrenin.

**RENAL THRESHOLD**

The level of blood sugar at which it begins to appear in the urine; normally low in some people and in pregnancy, high in diabetics of long standing.

**RENIN**

An enzymatic protein prominent in hypertension which forms a pressor substance with a globulin of blood serum (see angiotonin). See Oxyrenin.

**RENNET**

See Rennin.

**RENNIN**

Chymosin; enzyme from the glandular layer of stomach of a calf; coagulates milk proteins; used by diabetics to convert glucose of food to lactic acid.

**REPAIR, TYPES OF**

See Wound Healing.

**RESECTOSCOPE**

See Urology.

**RESOLVING POWER**

See Protoplasm.

**RESORCINOL, TESTS FOR**

See Krauskopf-Ritter, Revillon Reactions.

**RESPIRATION**

(1) The sum total of chemical reactions in living cells which release energy; (2) The aggregate of those processes by which oxygen is introduced into the system and carbon dioxide removed (Elvehjem).

**RESPIRATION**

The dynamic equilibrium (see Digestion), in which all living organisms maintain themselves, demands a steady supply of substances to the body cells. In these, the food (or partially split food) molecules are changed to release energy and to form other molecules useful in building the body tissues. The chemical changes (metabolism) which result in useful products mostly involve little energy gain or loss; the products may be larger molecules than the reactants; and any oxidation or reduction which does occur is between carbon containing molecules. The changes which release large amounts of energy for cellular use, on the contrary, depend on the complete or nearly complete disruption of the food molecules due to their oxidation by oxygen.

This burning of foodstuffs by oxygen in the cells is sometimes called internal respiration (as the partial oxidation and reduction of sugar molecules by each other or

their products, which also yields some free energy, is called fermentation). It is however, a phase of cell metabolism and need not be considered further here. What is important now is that large amounts of oxygen, as of food, must continuously be carried to the cells by the blood; and that the carbon dioxide formed as the foods are oxidized must be carried from them. Special mechanisms are present in the blood—hemoglobin to combine with oxygen and a reserve of alkali to combine with carbon dioxide—which enables this fluid to carry far more of both gases than could an equal amount of water. This duty is referred to as the respiratory function of the blood. But respiration proper, or breathing, or external respiration when paired with internal respiration, has to do only with the exchange of oxygen and carbon dioxide between the outside medium and the body.

This exchange ultimately depends, in all cases, on simple diffusion of each gas from a region in which its concentration (or, better, its partial pressure) is higher—oxygen outside the body, carbon dioxide inside—to a region in which its concentration is lower. In the simplest organisms, the unicellulars and the loosely built multicellulars like the sponges, no more is needed. Larger or more compact bodies of massed cells require a circulating fluid, some sort of blood or sap, to distribute the gases between the surface of exchange with the outside and the deeper cells and tissues. (The insects, however, use a completely separate set of air tubes to supply the cells.) Further, since volume increases as the cube of linear dimensions and surface only as the square, the surface of ex-

change must itself eventually be augmented by some sort of folding or pouching. Finally, as this surface becomes more complex, means must be found for insuring an adequate renewal there of the external medium, as well as of the internal fluid.

In water-living animals, the membrane for gas exchange is turned out and projects into the outer medium. Finger-like or leaf-like folds of an especially thin membrane are extended from the main body wall as gills. They are largely filled with fine capillary blood vessels, to renew the medium inside them; and they either wave about in the water (marine worms, salamanders, etc.) or regularly move in-and-out along with mouth movements (fish), to renew the outside medium.

In land-living air-breathing animals, the reverse solution has been reached. The exchange membrane has been turned in, not out, and more or less subdivided sacks of air, the lungs, enter the body mass from the main body wall. This necessitates even more elaborate devices for renewing the outside medium, the air, in these lung sacks; and many special muscles, bones and other structures are devoted to the required bellows-like movements of the body wall. In each case, air or water, the alternate solution would not work. Gills dry out in air but not in water; lungs allow air but not the far denser water to pass freely through their fine-tubed passages.

The lungs of mammals constitute myriad microscopic air sacks, the alveoli, set like grapes on their stems at the ends of fine air tubes, the bronchioles. Still like a bunch

of grapes, these passages join into ever larger twigs until, finally, a right and a left bronchus fuse to form the trachea, or wind pipe. This opens above through the voice box (larynx), a later addition, into the nose and back of the mouth. Each lung is sheathed in a smooth slippery coat, the pleura, which turns back on itself to line the chest wall and the diaphragm muscle. The latter forms the floor of the chest cavity, as the ribs and the muscles between them (intercostal muscles) form its sides and dome over its top. The lungs proper possess no muscle—they are elastic and collapse when the chest wall is opened—so all their movements are a passive following of the thorax (chest) in which they lie.

Inspiration—of a quart of air normally, of four times this on exertion—depends on the chest cavity enlarging as the ribs are pulled out and up by the intercostal muscles; and the diaphragm, which normally bows up in the center and is attached at its circumference, is pulled down by its own contraction. Expiration normally results from relaxation of these muscles; but other muscles (mainly internal intercostals, which oppose the external intercostals) can cause an active expiration of an extra three quarts of air normally held in the lungs. Another two quarts remain even then. Forced expiration occurs normally in such acts as coughing, sneezing, blowing, or straining, and abnormally in asthma, pneumonia, or other diseases with difficult breathing.

The respiratory movements depend on muscle action, which is controlled by nerves—the intercostal nerves, a dozen on each side,

to the rib muscles; the phrenic nerves, one on each side, to the diaphragm. Since the intercostal nerves come from the whole length of the spinal cord in the back of the chest and the phrenic nerves come from the spinal cord in the neck, and since all these must be properly coordinated if breathing is to be effective in exchanging the lung air, a special region of the nervous system acts as a control center for the lot. This respiratory center (in the medulla of the brain) sends out messages for each normal inspiration and each forced expiration. It is under voluntary control—it is possible, within limits, to hold the breath or breathe rapidly—but ordinarily sends out its regular signals without attention. It is controlled mainly by the amount of carbon dioxide reaching the brain—more of this in the blood leads to increased respiration which, of course, tends to get rid of the excess carbon dioxide. It is also controlled reflexly by sensory nerves—the vagus from the pleura is stimulated as the lungs stretch on inspiration and its impulses stop the inspiratory discharge of the respiratory center before this goes too far. Similar reflexes are responsible for coughing, and the like.

In respiration, then, fresh outside air (or water) is kept in contact with a thin much-folded membrane by the respiratory movements. The blood within this membrane is kept circulating by the heart. Since oxygen is continuously removed from the blood (and carbon dioxide added to it) by cell metabolism, the oxygen in the blood is kept at a lower pressure (and carbon dioxide at a higher pressure) than that in the air in the alveoli. Simple diffusion across the extensive perme-

able membrane completes the gas exchange.

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University of Chicago.

#### RESPIRATION— PHOSPHORYLATION COUPLING

See Creatine and Creatinine Metabolism.

#### RESPIRATORY CENTER

See Respiration.

#### RESPIRATORY PIGMENTS

Oxygen carriers of various bloods, which are colored (so far as investigated) which react reversibly with oxygen and are specifically adapted to carry as large an amount of oxygen as possible at the oxygen tension of the environment; e.g. hemoglobin, chlorocruorin, hemocyanin, hemerythrin, actiniohematin, heliocorubin.

#### RESPIRATORY QUOTIENT

The ratio between CO<sub>2</sub> output and O<sub>2</sub> intake. To a large extent it is an indication of the type of food used, as R.Q. for fat is 0.70-0.71; carbohydrates 1.0; protein 0.80-0.82. It is used in indirect calorimetric measurements.

#### RESTING POTENTIAL (CURRENT)

See Potentials, Bioelectric.

#### RETENE

An aromatic hydrocarbon obtained from abiatic acid by dehydrogenation with S; 1-methyl-7-isopropyl phenanthrene; b.p. 390-394°.

#### RETICULIN

A scleroprotein found as fibres in reticular tissue. It is very resistant to the action of acids and alkalis. Pancreatic trypsin attacks it less readily than does pepsin.

**RETINENE**

Chromogen of the 'Visual Yellow' of the retina, insufficiency of which causes 'night blindness.' Closely related to Vitamin A.

**REVERSIBLE-DISSOCIABLE COMPONENT SYSTEM**

See Sørensen's Reversible Dissociable Component System.

**REVERTOSE**

An old name for a disaccharide formed by enzymatic synthesis (1889).

**REVILLON REACTIONS FOR DIFFERENTIATING RESORCINOL AND HEXYLRESORCINOL**

Hexylresorcinol and resorcinol give different colors when treated with Denigès reagent, sucrose and sulfuric acid, ferric alum, ferric perchlorate, sodium carbonate, sulfuric and formic acids, and acetaldehyde.

Reference: Bull. soc. chim. biol. 1934, 305.

**REYNAL'S SPREADING FACTOR**

See Bacteriophage.

**rH**

A term representing the logarithm of the reciprocal of the pressure of the hydrogen gas in equilibrium with an oxidation-reduction system. Although Clark who introduced the term has advised against its continued use, it has found widespread entrance into the biological literature as a measure of the level of the oxidative or reductive intensity of biological redox systems. The latter should preferably be characterized by giving the Normal Potential ( $E_0'$ ) of the system at the pH obtaining during the measurements. (See article on Oxidation-Reduction).

**RHAMNEGIN**

See Xanthorhamnin.

**RHAMNETIN**

$C_{18}H_{12}O_7$ ; m.p. above  $300^\circ$ ; quercetin-7-methyl ether; the aglycone of xanthorhamnin; occurs in berries of Rhamnus cathartica.

**RHAMNICOSIN**

See Primeverose.

**RHAMNIN**

See Xanthorhamnin.

**RHAMNINOSE**

$C_{18}C_{34}O_{14}$ ; m.p.  $135^\circ$ ; a reducing trisaccharide consisting of one molecule of galactose and two of rhamnose; source Persian berries in which it is present as xanthorhamnin.

**RHAMNOASCORBIC ACID**

A synthetic substance which has about 1/5th the potency of ascorbic acid.

**l-RHAMNOSE**

$CH_3(CHOH)_4CHO$ ; isodulcitol; a methyl aldopentose, a constituent of many glycosides; non-fermentable, m.p. hydrate  $94^\circ$ .

**RHEIC ACID**

See Rhein.

**RHEIN**

Rheic or parietic acid, rhubarb yellow; dihydroxyanthraquinone-carboxylic acid,  $C_{15}H_8O_6$ ; m.p.  $321-322^\circ$ ; from Chinese rhubarb and senna leaves; used as purgative.

**RHEINBOLDT TEST FOR MERCAPTANS**

The test solution is poured over some sodium nitrite and some dilute hydrochloric acid or glacial acetic added. An intense red color is given by primary and secondary aliphatic mercaptans; in dilute



solution, tertiary aliphatic or aromatic mercaptans give a green color, in concentrated solutions a dichroic green color.

Reference: Ber. 59, 2600 (1926); 60, 184 (1927).

# **RHEOCHRYVIN**

A glucoside,  $C_{22}H_{22}O_{10}$ , from root of Chinese rhubarb; m.p. 211°.

# **RHEOPEXY**

Rapid solidification shown by a few thixotropic systems, induced by giving a slow circular to-and-fro motion to the sol.

# **RHEOTROPISM**

Reaction of a living form to the electric current.

# **RHEUMATIC FEVER**

See Fever Therapy.

# **RHIZOCALINE**

See Plant Growth Hormones, Phytohormones.

# **RHIZOPODA**

See Protozoa.

# **RHIZOPUS**

See Microbiology.

# **RHODANILIC ACID**

A modification of Reinicke's salt. Forms an insoluble complex with proline but not oxyproline. It is:  $[Cr(CNS)_4(C_6H_5 \cdot NH_2)_2]H$ .

# **RHODEOSE**

See d-Fucose.

# **RHODINAL**

See Citronellal.

# **RHODINOL**

See Citronellol.

# **RHODOPSIN**

Visual purple; chromoprotein of the retina, insufficiency of which causes 'night blindness.' Consists of a protein and a Vitamin A derivative. On heating or subjecting it to light it is converted to 'visual yellow'.

# **RHODOVIOLASCIN**

See Carotenoids.

# **RHODOXANTHIN**

See Carotenoids.

# **RHOEADINE**

$C_{21}H_{21}O_6N$ ; m.p. 256-257°; also given as 232°; alkaloid of the red poppy or corn poppy.

# **RHUBARB**

Rhizome and roots of various species of rheum; used as cathartic, bitter tonic, stomachic.

# **RHUBARB YELLOW**

See Rhein.

# **RHUS TOXICODENDRON**

See Poison Ivy.

# **RHYTHMIC GROWTH**

See Growth.

# **RHYTHM, PROTOPLASMIC**

See Protoplasm.

# **d-RIBITOL**

A sugar alcohol found in flavins, e.g. part of the structure of cytoflavin.

# **RIBOFLAVIN**

Vitamin B<sub>2</sub>; lactoflavin; Vitamin G; ovoflavin; 6,7-dimethyl isoalloxazine-9-d-riboside; m.p. about 275° with decomposition. The vitamin concerned with cell respiration as a constituent of Warburg's yellow respiration enzyme, and with other bodily functions. Deficiency in humans causes serious ill health, accompanied by a dermatitis and a gain in the water content of the tissues. It is found in meats, yeast, milk, greens, etc. The average dose is 3-5 mgm.

# **d-RIBOSE**

An aldopentose, with all the hydroxyl groups on the same side of the carbon chain, having a furanose configuration; constitu-

ent of nucleosides of plants and animals and of vitamin B<sub>2</sub>; m.p. 86° (also given as 95°).

# RICIDINE

See Ricinine.

# RICIN

An albumin found in the castor bean; agglutinates red blood cells and is highly toxic; used as a reagent for pepsin and trypsin.

# RICININE

C<sub>8</sub>H<sub>8</sub>O<sub>2</sub>N; 1-methyl-3-cyano-4-methoxy-2-pyridone; ricidine; slightly toxic alkaloid of castor oil seeds (*Ricinus communis*). Prisms, m.p. 201.5°, optically inactive, sol. hot water and alcohol; renders respiration more rapid.

# RICINOLEIC ACID

CH<sub>3</sub>(CH<sub>2</sub>)<sub>5</sub>CH(OH)CH<sub>2</sub>CH·CH(CH<sub>2</sub>)<sub>7</sub>COOH; an unsaturated monohydroxy fatty acid found in castor oil, m.p. 17°C. (also given as 4-5°); possibly the purgative principle of castor oil.

# RICINUS LIPASE

A fat hydrolyzing enzyme of the castor bean. Optimum pH for activity is 4.7-5.0.

See Enzymes, Non-Proteolytic.

# RICKETTSIA

See Microbiology.

# RICKETS

Rachitis; osteomalacia; a deficiency disease due to lack of vitamin D or indirectly of sunshine, showing most markedly in children. Bone changes show weakening and deformation. Osteomalacia is the adult form of the disease. Inorganic phosphorus in the blood is low. The treatment requires administration of foods rich in vitamin D, irradiated ergosterol, sunshine or artificial irradiation to activate skin sterols.

# RIEGEL-WILLIAM REACTION FOR PROCAINE, BUTYN, TUTOCAINE, BUTESIN, BENZOCAINE AND ORTHOFORM

The addition of a few drops of hydrochloric acid sodium nitrite solution and concentrated ammonia to a solution of 1 mg. of the substance in 1 cc. water gives an intense yellow color; this may be used for the colorimetric estimation of procaine.

Reference: J.A.C.S. 48, 4871 (1926).

# RIGG'S DISEASE

See Pyorrhea.

# RIGOR MORTIS

Rigidity of muscles in death due to myosin gelation.

# RIVANOL

2-Ethoxy-6,9-diaminoacridine-lactate; used as bactericide, antiseptic; externally in acute abscesses, furuncles and other localized purulent processes.

# RIVAT REACTION FOR OXYHEMOGLOBIN

The test solution is treated with 2 drops of an alkaline phenolphthalein solution and a drop of 0.5% manganous albuminate solution. A rose-red color is obtained, changing to violet-red in about a minute. An excess of the albuminate must be avoided.

Reference: Lyon Med. October 1911.

# ROBININ

A chromo-glucoside from flowers *Robinia pseudacacia*, melting at 195-197°.

# ROBINOSE

A reducing trisaccharide found in the glycoside robinine. Consists of two molecules of rhamnose and one of galactose.

**ROBISON-EMBDEN ESTER**

An equilibrium mixture of 70% glucosemonophosphoric acid and 30% fructosemonophosphoric acid, found in muscles as an intermediate of hexose metabolism. It is formed reversibly from hexosediphosphoric acid (Harden-Young ester) by enzymatic hydrolysis in the presence of Mg ions.

**ROBISON ESTER**

Glycopyranose-6-monophosphate, present in muscle and in fermentations.

**RODS AND CONES**

Elements of nerve cells of retina, the former containing visual purple for sensitivity and the latter serving for color discrimination.

**ROJAHN-STRUFFMAN REACTIONS**

See *Digitalis*.

**ROMIEU REACTION FOR LECITHIN**

Freshly prepared egg or brain lecithin appears colorless in a thin film on glass. The addition of dilute hydrochloric acid and a concentrated iodine-potassium iodide solution produces a mahogany-brown or garnet color reminiscent of glycogen in the same test.

By warming the film gently with 10% hydrochloric acid, glycogen is partially hydrolyzed and dissolved, differentiating it from lecithin.

Reference: *Compt. rend.* 184, 1206 (1927).

**ROOT FORMATION**

See *Plant Growth Hormones*.

**ROOTING OF CUTTINGS**

See *Plant Growth Hormones*.

**ROPY MILK**

The result of a mucus fermentation of milk by a coccus.

**ROSENBERG TEST FOR BILE PIGMENTS IN URINE**

A green color is obtained when 10 cc. of urine are treated with 10 cc. 20% potassium hydroxide solution and 2-3 drops of 10% copper sulfate solution.

**ROSENHEIM-CALLOW REACTIONS FOR STEROLS**

Reagent—Solution of 25 gm. of mercuric acetate in 100 cc. nitric acid, sp. gr. 1.42. Equal volumes of reagent and a chloroform solution of the sterol are mixed and shaken immediately.

Allo-cholesterol, allo-sitosterol, cholesterolene and  $\beta$ -cholesterol give red colors while a blue following a transient pink is given by ergosterol and its esters.

Reference: *Biochem. J.* 25, 74 (1931).

**ROSENHEIM-DRUMMOND TEST FOR VITAMIN A**

One drop of liver oil, dissolved in petroleum ether, is treated with 1 cc. of arsenic trichloride and shaken; a blue color is obtained, changing to purple in a few seconds and becoming paler. This may be used for the colorimetric estimation of the vitamin.

Reference: *Biochem. J.* 19, 753 (1925).

**ROSENHEIM REACTION**

A test for tryptophane. A very dilute solution of formaldehyde is added to the solution to be tested, and sulfuric acid stratified under the mixture. A purple junction ring is positive. The test is made more sensitive by the addition of 5 mg. of potassium nitrite to 100 cc. of sulfuric acid.

**ROSENHEIM REACTION FOR CHOLINE**

A solution of choline-platinic chloride in 15% alcohol is evapo-

rated to dryness and then treated with iodine-potassium iodide solution; large, dark brown dichroic and birefractive crystals of choline periodide are formed.

Reference: J. Physiol. 33, 220 (1905).

#### ROSENHEIM REACTION FOR ERGOSTEROL OR ITS ESTERS

When 1 mg. of ergosterol is brought into contact with 0.5 gm. of chloral hydrate (previously liquefied) a carmine red color is produced. Anhydrous chloral does not react. Concentrated aqueous trichloroacetic acid solution gives a red color changing to blue, with ergosterol in chloroform.

Reference: Biochem. J. 23, 47 (1929).

#### ROSENHEIM REACTION FOR OXYCHOLESTEROL

An immediate purple color is obtained when oxysterol is moistened with dimethyl sulfate; cholesterol remains unchanged.

Reference: Biochem. J. 1914, 74; 1916, 176.

#### ROSENHEIM REACTION FOR PROTEINS

Reagents — Formaldehyde solution, 1:2500. Pure sulfuric acid containing a few mg. of ferric chloride per 100 cc.

A purple contact ring is obtained when the solution of sulfuric acid is stratified beneath the protein-containing formaldehyde solution. The reaction is due to the presence of the tryptophane group. This is a modification of the Adamkiewicz reaction.

Reference: Biochem. J. 1, 233 (1906). Zeit. Untersuch. Nahr.-u. Genussm. 16, 231.

#### ROSENTHAL-ERDELYI TEST FOR VITAMIN A

Reagents — (a) 0.5% absolute

chloroform solution of pyrocatechol.

(b) cold saturated absolute chloroform solution of antimony trichloride.

1-2 cc. of an absolute chloroform solution of the oil is mixed with 1 cc. of (a) and 2-3 cc. of (b), and the tube heated in a water bath at 60° for 1-2 minutes. A potassium permanganate color is produced which is compared with a standard 0.01% permanganate solution.

Reference: Biochem. Zeit. 271, 414 (1934).

#### ROSENTHAL REAGENT FOR HEPATIC FUNCTION TEST

1. Sodium salt of tetrabromphenolphthalein sulfonic acid.

2. Disodium salt of phenoltetrachlorophthalein.

Reference: J. Pharmacol. 19, 385 (1922).

#### ROSIN

The commercially important resin obtained as a residue after distilling off the volatile oils of the oleoresin of American pines; colorless; yellow resin; abietic anhydride; used medically as rubefacient in ointments and plasters.

#### ROTENONE

$C_{23}H_{22}O_6$ , the principal active constituent of derris root, cubé, etc., m.p. 163°; highly toxic to insects but not to man or animals (1 part in 20 million will kill a goldfish in 3 hours).

#### ROTENONE TESTS

See Jones-Smith, Pozzi-Escot.

#### ROT-PROOFING

See Cellulose Decomposition.

#### ROTTLERIN

An amaroid from Rottlera tinctoria having a slight anthelmintic effect.

**ROUNDWORM**

See Worms, Intestinal.

**R. Q.**

Respiratory Quotient.

**RUBERYTHRIC ACID**

$C_{26}H_{28}O_{14}$  or  $C_{25}H_{26}O_{13}$ ; rubianic acid; a glycoside of the roots of *Rubia Tinctorum* (madder). Consists of glucose and alizarin. Crystallizes as citron-yellow needles or prisms from water, m.p. 258-60°.

**RUBIADIN**

$C_{21}H_{20}O_9$ ; m.p. about 270°; a glycoside of 2:4-dihydroxy-3-methyl anthroquinone, found in root of *Rubia Tinctorum*.

**RUBIANIC ACID**

See Ruberythric Acid.

**RUBIXANTHIN**

A carotenoid found in Rose leaves. Its structure is 3-hydroxy- $\beta$ -carotene- $\beta'$ -lycopene.

**RUFF'S METHOD**

A method for removing a carbon atom from a sugar. The aldose is oxidized to the acid, the calcium salt of which, on treatment with hydrogen peroxide loses carbon dioxide.

**RUSSMANN REACTION FOR ADRENALINE**

Four cc. of slightly acid adrenaline solution are treated with 1 drop of cold saturated mercuric chloride solution, 3 drops cold saturated sulfanilic acid solution and 1 cc. potassium biiodate solution. A brown color is obtained when the solution is boiled for 1 minute.

Reference. Klin. Wochschr. 1922, 654. Zeit. ges. exptl. Med. 32, 448 (1923). Compt. rend. soc. biol. 110, 564 (1932).

**RUST**

Parasitic fungi on plants.

**RUTAECARPINE**

An alkaloid,  $C_{18}H_{13}ON_3$ , from fruit of *evodia rutaecarpa*; m.p. 260-262°.

**RUTIN**

$C_{27}H_{32}O_{16} \cdot 2H_2O$ ; melin; phyto-melin; osyritin; violaquercitrin; myrticolorin; eldrin; a glycoside of the leaves of *Rista graveolens*, rue, tobacco, tomato stems, and many flowers; consists of glucose, rhamnose, and quercetin, which see. Forms bright yellow needles from water, m.p. 190°C.

## S

### SABADILLINE

An alkaloid,  $C_{34}H_{53}O_8N$ , from sabadilla seed; melting at  $200^\circ$ .

### SABADINE

An alkaloid,  $C_{29}H_{51}O_8N$ , from Sabadilla seed; m.p.  $238-240^\circ$ .

### SABINENE

A dicyclic monoterpene; d-form found in oil of savin, etc.

### SABINOL

A dicyclic monoterpene alcohol, found in oil of savin (d-form).

### SABINIC ACID

$C_{12}H_{24}O_3$ ; a saturated monohydroxy fatty acid found in conifer wax.

### SACCHARASE

Sucrase. See also Enzymes, Non-Proteolytic.

### d-SACCHARIC ACID

An oxidation product of glucose. It forms a slightly soluble salt with one molecule of KOH, which reaction is the basis of a test for glucose;  $COOH-(CHOH)_4-COOH$ ; m.p.  $125-126^\circ$ .

### SACCHARIN TESTS

See Börnstein.

### SACCHAROMYCETES

See Microbiology.

### SACCHAROSE

Obsolescent term for sucrose.

### SACURANIN

A glucoside from bark of *Prunus yedoensis* with no pronounced physiological action.

### SAH-MA REAGENT FOR ORGANIC HALIDES

When potassium - 3 - nitrophthalimide is refluxed with organic halides, well-crystallized sharp melting derivatives are obtained. Reference: Ber. 65B, 1630 (1932).

### SAFROL

3,4-Methylenedioxy-allylbenzene; constituent of various oils, notably that of sassafras; m.p.  $11^\circ$ ; b.p.  $232-234^\circ$ ; used instead of oil sassafras in subacute rheumatism; externally in pediculosis and ringworm; an insecticide.

### SAKAGUCHI REACTION FOR GUANIDINE

After conversion to the carbonate, the guanidine is evaporated with a little water and 1:2 glyccoll. The glycocyamine formed can be detected with  $\alpha$ -naphthol and sodium hypochlorite solution. Reference: J. Biochem. (Japan) 5, 25 (1923).

### SAKAGUCHI TEST

A test for a free guanidine group. A protein containing arginine or arginine itself will give the test. Treat the material with NaOH solution  $\alpha$ -naphthol, and then sodi-



um hypochlorite. An intense red color is positive. If specific conditions are followed, the test may be used for quantitative colorimetric determinations.

# SALICIN

$C_{13}H_{18}O_7$ ; salicyl alcohol glucoside; a glycoside from the bark of the willow and poplar; consists of glucose and saligenin. Colorless leaflets, m.p.  $201.5^{\circ}C$ .; used medicinally as antirheumatic and for neuralgia, chorea, etc.

# SALICYL ALCOHOL

See Saligenin.

# SALIGENIN

$C_7H_8O_2$ ; salicyl alcohol; saligenol; o-hydroxybenzyl alcohol; a hydrolytic product of the glycoside, salicin; local anaesthetic and remedy for rheumatism; m.p.  $86-87^{\circ}$ .

# SALIGENOL

See Saligenin.

# SALINIGRIN

A glucoside, constituent of various willow barks.

# SALIVA

Secretion of the parotid glands containing an amylase (ptyalin) and a mucin.

# SALKOWSKI REACTIONS FOR CHOLESTEROL

I. A few cgm. cholesterol in 2 cc. chloroform is treated with 2 cc. concentrated sulfuric acid. The sulfuric acid shows a green fluorescence, the chloroform becomes blood-red. When a few drops of the chloroform solution are placed in an evaporating dish, the solution rapidly becomes blue, green and finally yellow.

II. A solution of a trace of cholesterol in chloroform is allowed to evaporate from filter paper, giving a lemon-yellow color when the

spot is touched with a drop of sulfuric acid.

Reference: Zeit. anal. Chem. 11, 43 (1872). Zeit. physiol. Chem. 57, 523. J.A.C.S. 28, 391 (1906). J. Med. Research 1912, 531. Zentr. allgem. Path. 35, 314 (1924).

# SALKOWSKI REACTION FOR INDOLEACETIC ACID

A solution of indoleacetic acid, acidified with hydrochloric acid, is boiled with ferric chloride solution. A cherry-red color is obtained, sensitivity—1:100000. A violet color is produced with very dilute solutions of the acid.

Reference: Zeit. physiol. Chem. 9, 23.

# SALKOWSKI REACTION FOR INOSITOL

A trace of the substance, dissolved in nitric acid, sp. gr. 1.2, is treated with 1 drop of 10% calcium chloride solution and 1 drop of 1% platonic chloride solution. The solution is cautiously evaporated by blowing air over it; a rose-red to brick-red color is formed.

Reference: Zeit. physiol. Chem. 69, 478 (1910).

# SALKOWSKI TEST FOR BILE PIGMENTS

The icteric urine, alkaline with sodium carbonate, is treated with calcium chloride solution; after filtration the precipitate is dissolved in alcohol containing hydrochloric acid and heated. Bile pigments give a green to blue color.

Reference: Zeit. physiol. Chem. 4, 134. Zeit. anal. Chem. 17, 523; 25, 458. J. pharm. chim. 1905, 487. Deut. Med.-Ztg. 1911, 357.

# SALKOWSKI TEST FOR PROTEINS

A few cc. of formaldehyde solu-

tion (1:55000 to 1:50000) is treated with an equal volume of concentrated hydrochloric acid, 3 drops of 3% ferric chloride and 0.1 gm. of protein are added and the solution heated to boiling. A violet color changing to deep violet-blue is obtained. This reaction is given by all proteins containing tryptophane.

Reference: Zeit. physiol. Chem. 1920, 49. Schweiz. Apoth.-Ztg. 1922, 264.

#### SALKOWSKI TEST FOR SILICIC ACID IN URINE

After partial evaporation, the urine, in a cylinder is precipitated with alcohol. The sticky precipitate is washed several times with alcohol and ether. It is digested with cold, 1:3 hydrochloric acid, filtered on ashless filter paper and ignited. The residue is almost pure silicic acid.

Reference: Zeit. physiol. Chem. 83, 143 (1913).

#### SALMINE

A protamine found in the sperm and testicles of the salmon, which hydrolyzes almost entirely to arginine.

#### SALTING OUT

The addition of a solid salt, or a concentrated solution of a salt to a solution or a colloid, causing the solute (liquid or solid) or the disperse phase to separate out. In colloids this is due to the neutralization of the micellar charge by an ion of the added salt. In liquid-liquid systems, the phenomenon takes place only if the salt is soluble in just one of the liquids. If salt is added to an aqueous solution of a gas the solubility of the gas is decreased, the smaller the salt molecule the greater the effect.

#### SALVININ

See Pelargonin.

#### SAMADERIN

A glucosidal-amaroid,  $C_{29}H_{34}O_{11}$ , from the bark of *Samadera indica*; paralyzes the heart and brings it to a systolic standstill.

#### SAMBUNIGRIN

A glycoside of *Sambucus niger*; m.p., 151-152°; consists of glucose and l-mandelonitrile; diuretic, sudorific and alterative.

#### SANCHEZ REACTIONS FOR ALANINE

I. 0.01 gm. alanine are heated with 20 drops of 1% potassium permanganate solution at 100° for 1 minute, cooled, treated with 0.05 gm. oxalic acid until decolorized. 2 cc. alcohol, 0.02-0.03 gm. o-nitrobenzaldehyde and 10 drops 10% sodium hydroxide are added and the whole shaken with chloroform. The chloroform becomes blue.

II. The alanine and sodium hypochlorite are heated for several seconds, 2 drops of 30% sodium hydroxide are added and iodine-potassium iodide solution added dropwise; a precipitate of iodoform is obtained.

III. Dry alanine is vaporized in a closed tube, cooled and dissolved in dilute hydrochloric acid; the solution gives a reddish brown color with Bouchardt's reagent, a red precipitate with Dragendorff's reagent, and a white precipitate with Sanchez' molybdate reagent.

Reference: *Semana med.* (Buenos Aires) 1931, 651.

#### SANCHEZ REACTIONS FOR CYSTINE

I. A mixture of 0.1-0.2 mg., 3 drops 10% sodium nitrite solution and 2 drops hydrochloric acid

heated. After dilution with a few cc. water, extraction with ether and evaporation of the ether, an orange color is obtained with alkali hydroxides.

II. Cystine gives a precipitate of iodoform when heated with sodium hydroxide and iodine-potassium iodide solution.

Reference: *Semana med.* (Buenos Aires) 1930 II. 31.

#### SANCHEZ TEST FOR CHOLINE AND LECITHIN

The nuclear choline molecule is converted into iodoform by iodine-potassium iodide and sodium hydroxide.

0.1 gm. lecithin is boiled with 10 cc. 5% sodium hydroxide for 5 minutes, cooled, and 0.5% sulfuric acid added dropwise until acid. The fatty acids are filtered through a wet paper. 1 cc. of the aqueous filtrate can be used for carrying the above reaction.

Reference: *J.A.M.A.* 1930, 1057.

#### SANCHEZ TEST FOR CREATININE

0.02-0.03 gm. of substance are boiled with 2 cc. water and 0.5 gm. mercuric oxide. The decanted liquid is treated with 0.5 gm. resorcinol and 2 cc. sulfuric acid are added without mixing. A blue color is formed at the contact zone.

Reference: *Semana med.* (Buenos Aires) 1930, II, 616.

#### SANGUINARINE

An alkaloid,  $\psi$ -Chelerythrine,  $C_{20}H_{15}O_5N$ ; m.p. 240-265° (depending on speed of heating); from roots of *Papaveraceae*.

#### SANTALENE

Sesquiterpenes; alpha-form and beta-form found in Indian sandalwood.

#### SANTALOLS

Alpha and beta forms of a sesquiterpene alcohol found in Indian sandalwood oil.

#### SANTENE

A terpene-like hydrocarbon,  $C_9H_{14}$ , found in sandalwood oil and in some pine oils, b.p. 140°.

#### SANTENONE

A saturated dicyclic ketone; 1-form found in sandalwood oil.

#### SANTONIN

A lactone,  $C_{15}H_{18}O_3$ , m.p. 169-171°, having a structure of three cycles, active principle of wormseed (*Santonica*); a vermifuge for roundworms and threadworms but not tapeworms; average dose 0.06 gm.

#### SAPOGENIN

The nucleus of the non-sugar residue of the saponins.

#### SAPONARIN

A glucoside from leaves of *Saponaria*,  $C_{21}H_{24}O_{12} \cdot 2H_2O$ .

#### SAPONIFICATION

(1) The hydrolysis of fats by alkalis, forming glycerol and the alkali salts of the fatty acids.

(2) Sometimes the definition is extended to include any ester hydrolysis, whether by alkali, acid, steam, or enzyme.

#### SAPONIFICATION NUMBER

The number of milligrams of KOH needed to saponify 1 gram of a fat or oil.

#### SAPONINS

Glycosides which have sapogenin as the non-sugar component; make strongly foaming aqueous colloids; include various types, e.g. sarsasapogenin, smilagenin, henderagenin. Some are strong fish poi-

sons and hydrolyze red blood cells easily.

See Steroids.

# SAPONIN TEST

See Kobert, Vestlin.

# SAPROPHYTE

Organism living on organic decay.

# SARCODE

An old term for protoplasm (Dujardin 1835).

See Protoplasm.

# SARCOLACTIC ACID

See d-Lactic Acid.

# SARCOLOBID

A glucoside from inner bark of *Sarcolobus narcoticus*; a curare-like spastic poison.

# SARCOSIN(E)

Methyl glycine, m.p. 212°, product of alkaline hydrolysis of creatine.

# SARMENTOSE

A desoxymethyl pentose, obtained from sarmentocymarin, a glycoside.

# SARSASAPOGENIN

A component of the glycoside sarsasaponin, which is a sterol;  $C_{27}H_{44}O_8$  (Sobotka); m.p. 199-200°; occurs in sarsaparilla, smilax, etc.

# SARSASAPONIN

A saponin of sarsaparilla root and foxglove; consists of 3 molecules of glucose and one of sarsasapogenin.

# SASAKI REACTION FOR GLYCINE ANHYDRIDE AND OTHER DIKETOPIPERAZINES

Glycine anhydride, when boiled with the Jaffe creatinine reagent (saturated solution of picric acid and sodium carbonate), gives rise to a red color.

Reference: Biochem. Zeit. 114, 63 (1921).

# SCABIOSIN

A glucoside from root of *Scabiosa succisa* melting at 108-110°.

# SCAR TISSUE

See Wound Healing.

# SCAEVOLIN

An amaroid from bark and leaves of *Scaevola Königii*; said to be slightly toxic.

# SCHALL REAGENT FOR ULTRA-VIOLET RAYS

p-Phenylene diamine paper is colored blue by ultra-violet rays, while sun rays have no effect.

Reference: Süddeut. Apoth.-Ztg. 1908, 738.

# SCHARDINGER ENZYME

See Xanthine Oxidase.

# SCHERINGA REACTION FOR NEOARSPHENAMINE

A 1:1000 aqueous neoarsphenamine solution turns violet upon the addition of concentrated ammonium persulfate solution.

Reference: Pharm. Ztg. 1923, 401.

# SCHICK TEST FOR DIPHTHERIA IMMUNITY

A 1:500 toxin solution in physiological saline, preserved with 0.5% phenol is used for an intracutaneous reaction, using a dose 1/50 of the lethal dose for a guinea pig of 250 gm. weight. An area of redness and edema attaining a maximum in 48-72 hours, is produced at the injection site by patients whose blood contains insufficient antitoxin to neutralize the amount of toxin used.

Reference: Münch. Med. Wochschr. 1908, 504. J.A.M.A. 1921, 1254. Schweiz. med. Wochschr. 1922, 239.

See also Diphtheria.

**SCHIFF REAGENT FOR ALDEHYDES**

Aldehydes give a violet-red color when treated with a solution prepared by decolorizing a solution of 0.25 gm. of fuchsin in a liter of water with sulfur dioxide.

Reference: Ann. 140, 93 (1866). Ber. 13, 2342 (1880). Compt. rend. 64, 182; 105, 1182; 119, 75. J.A.C.S. 1906, 1619. J. Am. Pharm. Assoc. 1933, 1237.

**SCHIZOGENESIS**

See Fission.

**SCHIZOMYCETES**

See Microbiology.

**SCHMALFUSS-WERNER-KRAUL TEST FOR OXALIC ACID IN URINARY CALCULI**

A solution of the powdered material in 10% hydrochloric acid is filtered and extracted with ether; the ether extract is evaporated and 0.1-1 mg. of residue is gently fused with 0.4-2 mg. of resorcinol on white porcelain. After cooling the fusion is treated with a drop of concentrated sulfuric acid and heated several times for 3 seconds at 20 second intervals—a deep blue then a green color is formed.

Reference: Klin. Wochschr. 11, 791 (1932).

**SCHMIDT TEST FOR SULFANILAMIDE IN BLOOD**

An acid solution of sodium  $\beta$ -naphthoquinone-4-sulfonate is added to a tungstic acid blood filtrate, producing a straw-yellow to orange-red color which can be estimated colorimetrically.

Reference: J. Biol. Chem. 122, 757 (1938).

**SCHÖNLEIN'S DISEASE**

See Hemorrhagic Diatheses.

**SCHOORL MICRO-REACTIONS FOR CHOLINE**

Double salts are formed by the reaction of choline hydrochloride with the following: mercuric chloride and iodide, sodium-gold chloride, potassium bismuth iodide, picric acid and picrolonic acid.

Reference: Pharm. Weekblad 55, 363 (1918).

**SCHMIEDBERG REACTIONS**

See Digitalis.

**SCHOTTEN-BAUMANN REACTION**

The reaction of benzoyl chloride with amines in the presence of NaOH. With primary and secondary amines the product has the formula;  $R_1R_2CNHCOC_6H_5$ ; where the R's may be H or an organic radical. With tertiary amines one gets no reaction. In all cases one gets separable products, so that this is a means of identifying and separating amines.

**SCHULTE TEST FOR PENTAMETHYLENETETRAZOLE AND BLOOD**

A mixture of 50 cc. urine and 5 cc. 20% lead acetate solution is filtered and the filtrate saturated with ammonium sulfate and extracted with 20, 10 and 10 cc. of chloroform. After evaporation, the residue is dissolved in a small quantity of water and tested with cuprous chloride.

Reference: Pharm. Weekblad 75, 386 (1938).

**SCHULZ TEST FOR CACODYLATE IN URINE**

A few cc. of urine, treated with a small amount of crystalline phosphorous acid, gives rise to an odor of cacodyl oxide.

Reference: Analyse der Harn (1913) II, 1464.

**SCHUNTERMANN TEST FOR UROCHROMOGEN IN URINE**

Reagent—Mixture of concentrated sulfuric acid and a little sodium perborate. 2 cc. of urine are mixed with 1 cc. of reagent, cooled and shaken with 3 cc. ether. Ether layer becomes intense lemon-yellow color.

Reference: Beitr. Klin. Tuberkulose 65, 773 (1927).

**SCHWEITZER'S REAGENT**

Ammoniacal copper hydroxide, a solvent for cellulose.

**SCILLAIN**

A glucoside from the bulb of squill,  $(C_6H_{10}O_5)_x$ ; causes systolic heart standstill.

**SCILLAREN**

A mixture of the A and B forms in the proportion in which they naturally occur in squill, 2 of A to 1 of B; for use see Scillaren A and B.

See Digitalis.

**SCILLAREN A**

The crystalline constituent of the natural glucosides of squill; use as of digitalis.

**SCILLAREN B**

The amorphous constituent of the glucosides of squill; use as of digitalis.

**SCILLIPICRIN**

An amaroid, active bitter principle from bulb of squill; cardiac action like that of digitalis.

**SCILLITIN**

A glucoside,  $C_{17}H_{25}O_6$ , from squill; has been presumed to be the toxic constituent of squill.

**SCLERA**

See Eye, Biochemistry of.

**SCLEROPROTEINS**

See Albuminoids.

**SCLEROSIS**

Hardening; excess of connective tissue.

**SCOMBRINE**

A protamine found in the testicles of the mackerel.

**SCOPARIN**

A physiologically indifferent compound,  $C_{22}H_{22}O_{11}$ , from *Cytisus scoparius*, melting at 202-219°.

**SCOPOLAMINE**

See Hyoscine.

**SCOPOLETIN**

The aglucone of scopolin occurring in the root of *Scopolia japonica*; m.p. 204°.

**SCOPOLINE**

An alkaloid, a decomposition product of scopolamine, melting at 108-109°, boiling at 248°.

**SCUDI MICRO-TESTS FOR SULFANILAMIDE**

I. A mixture, on a microscopic slide, of 1 drop sulfanilamide solution, 1 drop 37% formaldehyde solution and 1 drop 10% sodium carbonate, is evaporated to dryness on a water bath. Residue is freed from soluble salts by extraction with 2 drop portions of water. Product melts at 235-240° C. with decomposition. Sensitivity—0.0012 mg.

II. One drop sulfanilamide solution and 1 drop iodine monochloride solution are evaporated to dryness; a drop of water is added to the residue, a second drop of hot water added, stirred and drawn off with absorbent filter paper. Alkali-soluble, water and acid-soluble needles are obtained, melting with decomposition at 265° C.

III. A solution of 1 drop concentrated hydrochloric acid and 1 drop sulfanilamide solution is



evaporated to dryness and treated with a small drop of saturated picric acid solution. Long yellow needles, m.p. 179-180° C. are obtained.

IV. One drop mercuric nitrate solution and 1 drop 10% sodium carbonate solution are added to 1 drop sulfanilamide solution, yielding a highly flocculated transparent white precipitate.

Reference: Ind. Eng. Chem. Anal. Ed. 10, 346 (1938).

#### SCUDI-RATISH METHOD FOR ASCORBIC ACID

Five cc. of a 5 mg. percent solution of sulfanilamide are treated with 1 cc. 0.05% sodium nitrite and 1 cc. of 20% sulfoscalicylic acid. After standing for 1-3 minutes, the solution is treated with 1 cc. of 1% urea. 10 cc. of fresh 10% acetic acid solution of the vitamin are added after 5 minutes. After another 5 minutes, 7.4 cc. of 1-dimethylnaphylamine solution (1 cc. diluted to 500 cc. with alcohol) are added and the solution is mixed. Between 10 and 50 minutes, the colors developed are compared with standards prepared by lowering the sulfanilamide concentration and replacing the vitamin with vitamin-free 10% acetic acid.

Reference: Ind. Eng. Chem. Anal. Ed. 10, 420 (1938).

#### SCURVY

Avitaminosis C; a deficiency disease due to lack of vitamin C, showing latency in vague symptoms turning to hemorrhages, anemia, bone weakening, etc. Tests have been developed for capillary fragility and the saturation of the blood and urine with vitamin C. Sources rich in vitamin C or pure ascorbic acid are ad-

ministered. Normal plasma ascorbic acid should run 0.70-1.0 mg. per 100 cc. If it is below 0.15 full scurvy sets in.

#### SCUTELLAREIN

See Scutellarin.

#### SCUTELLARIN

From flowers and leaves of *Scutellaria*; on hydrolysis gives glucuronic acid and scutellarein.

#### SCYLLITOL

One of the inactive inositols; old names, cocositol, quercin; present in some oaks, dog fish, etc.

#### SCYMOL

$C_{27}H_{43}O_5$ , m.p. 187°, a compound related to sterols found in shark bile as a sulphuric ester.

#### S.D.A.

See Specific Dynamic Action of Protein.

#### SEA ONION

See Squill.

#### SEBACIC ACID, ROLE IN PLANTS

See Plant Growth Hormones.

#### SEBORRHEA

Overactive secretion of the sebaceous glands.

#### SEBUM

The secretion of the sebaceous glands of the skin, mostly cholesterol esters and waxes.

#### SECRETIN

A hormone of the intestinal mucosa, which stimulates the pancreas to secrete digestive juices. A crystalline, basic protein, secretin (solution pH=7.5) with a molecular weight of 5000 has been isolated.

#### SECRETOGOGUE

A substance which promotes secretion, e.g. gastric secretion by gastrin or histamine.

**SEDIMENTATION POTENTIAL**

The potential difference induced between the top and the bottom of a liquid when particles are allowed to fall through the liquid.

**SEDOHEPTITOL**

See Volemitol.

**SEEDS, WATER CONTENT OF**

See Protoplasm.

**SELACHYL ALCOHOL**

Alpha-oleyl-glyceryl ether, b.p.  $242^{\circ}$  at 5 mm.; a constituent of elasmobranch liver oils.

**SELINENE**

A sesquiterpene of celery oil.

**SELIWANOFF REACTION FOR LEVULOSE AND SUCROSE**

When levulose or sucrose is heated with a hydrochloric acid solution of resorcinol, a red color is produced which precipitates a darker amorphous precipitate on cooling. This is soluble in alcohol with a pale red color. Carbohydrates yielding levulose on hydrolysis give this reaction.

Reference: Ber. 20, 181 (1887). Zeit. Biol. 1895, 322. Zeit. physiol. Chem. 1903, 555.

See also Glycosurias, Non-Diabetic.

**SELLARD'S TEST**

An approximate test of alkali reserve by the administration of sodium bicarbonate and testing the pH of the urine at intervals.

**SEMINASE**

See Enzymes, Non-Proteolytic.

**SEMI-PERMEABLE MEMBRANE**

A membrane that allows a selective passage of molecules through it. Semi-permeable membranes can be prepared that have graded

permeability, each one allowing only molecules of a certain maximum size to pass through it.

**SENECIFOLIDINE**

An alkaloid,  $C_{18}H_{25}O_7N$ , from *Senecio latifolius*, melting at  $212^{\circ}$ ; is toxic.

**SENECIFOLINE**

An alkaloid from *Senecio latifolius*,  $C_{18}H_{27}O_8N$ , melting at  $149-195^{\circ}$ ; is toxic.

**SENECINE**

An alkaloid from *Senecio vulgaris* and other allied compositae; in large doses attacks central nervous system, in small causes hemorrhages.

**SENEGIN**

Saponin-like glucoside from root of *Polygala Senega*; m.p. about  $240^{\circ}$ ; used as expectorant, emetic.

**SENNA**

Dried leaves and pods of *Cassia* species; strong purgative and cathartic; constituents are crysophanic acid, sennaemodin, sennarhamnetin, sennanigrin, cathartomannite; dose 2-10 gm.

**SENNITE**

See Pinitol.

**SENSE RECEPTORS**

See Nervous System.

**SENSIBAMINE**

See Ergot.

**SENSITIZERS (TO LIGHT)**

See Radiation, Biological Effects of.

**SEPIA**

Cuttle-fish bone; calcareous substance found under skin of back of *Sepia officinalis*, containing calcium carbonate and phosphate, and gluten; used as polishing agent and in tooth powders.

# SEPTENTRIONALINE

An alkaloid of doubtful composition; m.p. 131°; stated to have anaesthetic action; paralyzes respiration.

# SEQUOYITOL

Methyl ether of i-inositol from redwood, *Sequoia sempervirens*, m.p. 234°.

# L-SERINE

$C_3H_7O_3N$ ,  $\beta$ -hydroxy- $\alpha$ -amino propionic acid;  $CH_2OH \cdot CHNH_2 \cdot COOH$ ; levorotatory; large prisms, m.p. 228°C., with decomposition. An amino acid of the silk scleroprotein sericin. Can be synthesized by the organism, so is not essential in the diet. Possibly interchangeable with alanine.

# SERINE METABOLISM

Serine is oxidized to  $\alpha$ -keto- $\beta$ -hydroxy propionic acid in the body. Forms glucose in the diabetic.

# SEROLOGY

See Microbiology.

# SEROTIN

A glucoside from the leaves of the wild cherry.

See Flavonol Glycosides.

# SERTOLI CELLS

Lining epithelium cells, enlarged in connection with developing spermatozoa of testes.

# SERUM

The straw-colored liquid, sp. gr. 1.027 in man, obtained by removal of fibrinogen and cells from the blood, slightly more than 90% water. It is the solvent for the food, waste and metabolic products carried by the blood. See Blood and Plasma.

# SEWAGE DISPOSAL

See Cellulose Decomposition.

# SEX DETERMINATION TEST

See Manuiloff Reagents.

# SHAFFER TEST FOR

# $\beta$ -HYDROXYBUTYRIC ACID

The acid is oxidized to acetone by potassium dichromate and sulfuric acid; the acetone is detected by any of the well-known tests for it.

Reference: J. Biol. Chem. 5, 211 (1908)

# SHAW TEST FOR

# BLEACHED FLOUR

One kilo of flour is extracted with 95% alcohol for 4 hours. After evaporation of the extract, the residue is extracted with a mixture of equal volumes of ether and alcohol, filtered and evaporated to dryness. A diphenylamine solution in concentrated sulfuric acid is poured on the residue giving a blue color with flour bleached with nitrogen peroxide.

Reference. J.A.C.S. 1906, 687. Zentralhalle 1913, 248.

# SHELLAC

The resinous secretion of the insect, *Tachardia lacca*, contains aleuritic acid (q.v.).

# SHERMAN-MUNSELL

# VITAMIN A UNIT

That amount of vitamin A, which when fed six times a week, just suffices to support a gain of weight of 3 grams a week in a standard test rat for a period of 4-8 weeks.

# SHERMAN VITAMIN A UNIT

See Sherman-Munsell Vitamin A Unit.

# SHETERIN

A glucoside,  $C_{26}H_{30}O_{13} \cdot \frac{1}{2}H_2O$ , from the berries of *Rhamnus cathartica*.

# SHIGA ORGANISM

See Gastro-Enterology.

**SHIKIMIC ACID**

A trihydroxy-cyclohexane carboxylic acid, derived from *Illicium religiosum*.

**SHIKIMIN**

A glucosidal amaroid,  $C_7H_{10}O_6$ , from the fruit of *Illicium religiosum*, melting at  $175^\circ$ ; is toxic, belonging to the picrotoxin group.

**SICALOIN**

An amaroid,  $C_{14}H_{17}O_6(OCH_3)$ , from Sicilian aloe.

**SIGMOID**

See Gastro-Enterology.

**SILAGE**

Acid fermented fodder.

**SILICIC ACID TEST, IN URINE**

See Salkowski.

**SILURIAN ERA**

See Paleozoic.

**SIMON REACTION FOR  
PYRUVIC ACID**

The acid solution is treated with ammonia, then sodium nitropruside and heated gently. A blue-violet color forms which changes to orange on long standing.

Reference: *Compt. rend.* 1897, 534. *Bull. soc. chim. biol.* 6, 477 (1924).

**SIMON TEST FOR  
GLYCOGEN IN URINE**

A mixture of 90 cc. urine and 10 cc. 40% potassium hydroxide is filtered and the filtrate is treated with 10 gm. potassium iodide and 50 cc. 90% alcohol; a flocculent precipitate is formed.

Reference: *Pharm. Zentralhalle* 1898, 301.

**SINAPINE**

An alkaloid, the choline ester of sinapic acid; from black mustard seed.

**SINIGRIN**

$C_{10}H_{18}O_9NS_2K \cdot H_2O$ ; m.p. 126-

$129^\circ$ ; sinigroside; potassium myronate; a mustard seed glycoside hydrolysed by the enzyme myrosin to glucose, allyl isothiocyanate and K hydrogen sulfate.

**SINIGRINASE**

See Enzymes, Non-Proteolytic.

**SINIGROSIDE**

See Sinigrin.

**SINISTRIN(E)**

The fructosan of *Scilla maritima*; See Inulin.

**SINOMENINE**

$C_{19}H_{23}O_4N$ ; needles, two m.p.'s,  $160^\circ$  and  $182^\circ$ ; an alkaloid of *Sinomenium Acutum*, closely related to thebaine, used in rheumatism, large doses causing respiratory paralysis.

**SITOSTEROL**

Plant mixture,  $C_{29}H_{49}OH$ , m.p.  $137^\circ$ ; found in wheat, legumes, cocoa, corn, figs, beet oil, cotton seed oil, laurel oil. Consists of a mixture of at least 3 components in varying proportions depending on the source, and difficult to separate from each other.

**SKATOLE**

3-methyl indole; m.p.  $95^\circ$ ; b.p.  $265-266^\circ$ ; an amine formed by bacterial decomposition of tryptophane. Partly responsible for the odor of feces and decaying protein. Occurs also in beet root, nectandra wood and coal tar.

**SKATOLE TESTS**

See Legal, Montignie, Zappacosta.

**SKIMMIANINE**

An alkaloid,  $C_{14}H_{18}O_4N$ , from leaves of *Skimmia Japonica*, melting at  $175-176^\circ$ .

**SKIN, EFFECT OF RAYS ON**

See Radiation, Biological Effects of

**SLIME MOLD,  
SCLEROTIUM OF**

See Protoplasm, Microbiology.

**SMALLPOX**

Variola; infectious, contagious disease caused by a filterable virus, with characteristic symptoms of skin eruption, papules, vesicles, pustules crusts and permanent scars. Types: variola vera, hemorrhagic smallpox and mild smallpox. Vaccination immunity lasts only a limited time, about 10 years.

**SMILACIN**

See Parillin.

**SODIUM TEST**

See Kolthoff.

**SOIL BACTERIA**

See Cellulose Decomposition.

**SOILS, CLASSIFICATION OF**

See Agricultural Biochemistry.

**SOLANGUSTINE**

A gluco-alkaloid,  $C_{33}H_{53}O_7N_2 \cdot H_2O$ , from *Solanum angustifolium*, melting at  $235^\circ$ .

**SOLANINE**

A gluco-alkaloid of undetermined structure, obtained from potato sprouts and other Solanaceae.

**SOLANUM ALKALOIDS**

See Steroids.

**SOLM REAGENT FOR PEPSIN**

A solution of 0.5 gm. ricin in 50 cc. 5% sodium chloride solution is treated with 0.5 cc. of 0.1N hydrochloric acid after filtering. Pepsin, at  $40^\circ$ , clarifies the milky turbidity of the reagent.

**SOL, POLYDISPERSE**

A sol containing particles of varying sizes.

**SOLUBILITY, LIPID**

See Permeability.

**SOMATIC**

Pertaining to the body of an animal. A somatic cell is one that is not a gamete.

**SOMATOTROPIC HORMONE**

See Growth Hormone.

**SONNE ORGANISM**

See Gastro-enterology.

**SOPHORINE**

See Cytisine.

**SORBIC ACID**

$CH_3CH:CHCH:CHCOOH$ , m.p.  $133-134^\circ$ , found in the berries of *Sorbus aucuparia*.

**d-SORBITE**

See d-Sorbitol.

**d-SORBITOL**

d-sorbite; a hexahydroxy hexane, m.p.  $87-92^\circ$ , also at  $55^\circ$ ; obtainable by reduction of d-fructose and d-glucose. It is frequently found with d-mannitol and occurs in ripe mountain ash berries, cherries, plums, pears, apples, etc. On oxidation yields l-sorbose, which can be oxidized to vitamin C.

**SORBITOSE**

See d-Sorbose.

**d-SORBOSE**

Sorbitose; a ketose sugar formed by the bacterial oxidation of sorbitol by *Bacterium xylinum*; sweet non-fermentable, m.p.  $154^\circ$ , also given as  $165^\circ$ .

**SÖRENSEN'S REVERSIBLE  
DISSOCIABLE COMPONENT  
SYSTEMS**

A theory of protein structure. Long polypeptide chains are combined in varying amounts with other groups, also mainly polypeptides, the forces holding these

large groups together being residual valences.

### SØRENSEN TITRATION

A method for determining the carboxyl content of an amino acid mixture, by reacting the amino group with formaldehyde, thus allowing direct titration of the carboxyl group.

### SORGHUM

The name applied to a group of grasses (*Andropogon Sorghum*) from which sugar and sugary syrups may be prepared.

### SOYA OIL

Soy Oil, Soya Bean or Chinese Bean Oil; made up of glycerides of certain fatty acids; used in mfg. of soaps, paints, varnishes; used as illuminant and as food.

### SPARTEINE

Lupinidine;  $C_{15}H_{29}N_2$ ; b.p.  $326^\circ$ ; alkaloid of broom and yellow lupein seeds; resembles coniine and digitalis in action and is less toxic; used as diuretic in certain arrhythmias.

### SPASM

Involuntary muscular paroxysm; tonic, if uniform; clonic, if in waves.

### SPATHULATINE

An alkaloid,  $C_{33}H_{64}O_5N_4$ , from seed hulls of lupinus spathulatis, melting at  $227^\circ$ .

### SPEARMINT

Dried leaves and tops of *Mentha spicata* containing carvone as active principle; used as carminative, like peppermint.

### SPECIFIC DYNAMIC ACTION OF PROTEINS

The name applied to the increased metabolism observed when protein is fed. If a definite number of calories is fed to a dog which has

been fasting, the heat production is about 5% more than the caloric value of the protein. Originally this was thought to be due to cell stimulation by the protein, causing them to burn more fat and carbohydrate. However, a large portion of the heat can be attributed to the extra work done in disposing of the N of the protein. See Amino Acids, Physiology of.

### SPECIFIC DYNAMIC EFFECT

Same as calorogenic effect (see this).

### SPECIFIC ROTATION

A measure of the degree of optical rotation shown by a compound. Defined as the number of degrees of rotation of the plane of polarized light caused by a solution of 1 gram of a substance in 1 cc. of solution in a 1 decimeter tube.

### SPECIFICS (Drugs)

See Pharmacology.

### SPERMACETI

Cetaceum; m.p.  $42-50^\circ$ ; a waxy substance from the head of the sperm whale, mostly cetyl palmitate, esters of lauric, stearic and myristic acids and free cetyl alcohol; used as ointment base.

### SPERMATIDS

The immature male gamete cells arising from the division of the spermatocytes. They give rise to spermatozoa.

### SPERMATOCYTES

The immature male gamete cells arising from the division of the spermatogonia.

See Spermatids.

### SPERMATOGONIA

In the development of male gametes, the first cells arising from the primordial sex cells.

See Spermatocytes.



**SPERMIDINE**

$\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_4\text{NH}_2$ ; occurs in association with spermine in sperm and in animal organs.

**SPERMIN**

An obsolete name for the male sex hormone.

**SPERMINE**

$\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_4\text{NH}(\text{CH}_2)_3\text{NH}_2$ ; gerontine; musculamine; neuridine; strong base, a constituent of sperm (as phosphate), ox pancreas, yeast, etc.

**SPERM OIL**

From the sperm whale containing fatty acid esters, small quantities of spermaceti; saponification no., 123-147; Iodine no., 80-84; used as lubricant, in lamps, hardening steel, mfg. of soaps.

**SPHINGOMYELINS**

A group of phospholipids, m.p. ranging from  $196^\circ$  to  $198^\circ$ , occurring in the brain, kidney and liver along with cerebrosides. Sol. in water and most organic solvents except ether, cold acetone and cold alcohol. On hydrolysis they yield phosphoric acid, choline and sphingosine, and a fatty acid — either lignoceric, stearic, nervonic, or cerebronic acid.

**SPHINGOSINE**

$\text{CH}_3(\text{CH}_2)_{12}\text{CH}:\text{CHCH}(\text{NH}_2)\text{CH}(\text{OH})\text{CH}_2\text{OH}$ ; a basic component of the sphingomyelins and of cerebrosides.

**SPHYGMOGRAPH**

A recording instrument for pulse or pressure waves.

**SPINACENE**

See Squalene.

**SPINAL REFLEX**

See Neurophysiology.

**SPIRILLUM**

See Microbiology.

**SPIRIT OF AMMONIA**

A soln. of 10%  $\text{NH}_3$  in alcohol; formerly used as a diffusible indirect respiratory and circulatory stimulant; externally as counter-irritant.

**SPIRIT OF AMMONIA, AROMATIC**

A soln. containing 34 gm. ammon. carbonate, 90 cc. 10% ammonia water, 10 cc. lemon oil, 1 cc. oil of lavender, 1 cc. oil of myristica, 700 cc. alcohol, dilute by water to one liter; used as stimulant and locally in insect bites.

**SPIRIT OF ETHER**

A mixture of alcohol and ether made by diluting 325 cc. ether U.S.P. to 1000 cc. with alcohol; used as anodyne, carminative, indirect circulation stimulant, anti-spasmodic.

**SPIROCHAETALES**

See Microbiology.

**SPIROGRAPHISHAEM**

See Chlorocruorohaem.

**SPLEEN**

Largest ductless gland functioning in the formation and destruction of red blood cells and in the regulation of lymph.

**SPLENIC FEVER**

See Anthrax.

**SPONDYLITIS DEFORMANS**

A form of arthritis (which see) characterized by progressive vertebral deformity including thickening and calcification of the anterior spinal ligament.

**SPONGIN**

An albuminoid of the skeletons of the sponges and corals.

## SPORES

The minute reproductive bodies of all flowerless plants.

## SPOROZOA

See Protozoa.

## SPREADING FACTOR

See Microbiology.

## SPRINTILLAMINE

An alkaloid,  $C_{28}H_{45}O_4N$ , from rhizome of *Helleborus viridis*, melting at 228-229°.

## SPRINTILLINE

An alkaloid  $C_{25}H_{41}O_3N$ , from rhizome of *Helleborus viridis*, melting at 141-142°.

## SQUALENE

Spinacene;  $C_{30}H_{50}$ , an open chain triterpene found in elasmobranch livers; a mixture.

## SQUILL

Sea onion; the fleshy inner bulb scales of the white variety of *Urginea maritima*, used as expectorant, nauseant, diuretic; action also resembles that of digitalis.

## STACHYASE

See Enzymes, Non-Proteolytic.

## STACHYDRINE

$C_7H_{13}O_2H \cdot H_2O$ ; prolinbetaine; m.p. 235°, N-methylproline-methyl betaine, obtained from tubers of *Stachys tubifera* and leaves of orange tree.

## STACHYOSE

A tetrasaccharide, m.p. 167°, present in a number of plants, such as peas, ash manna, white jasmine twigs etc., yielding fructose and mannatriose on hydrolysis.

## STACHYTARPHIN

An amaroid from fresh leaves of *stachytarpheta dichotoma*.

## STAMM TEST FOR PEROXIDE IN ETHER

One drop of Meyer phenolphthalein reagent is mixed with 2 drops of 1:2000 copper sulfate solution followed by 1 drop of the ether. A pink to intense red ring is formed at the interface.

Reference: *Pharmaci* 1924 8. *Farm. Revy* 1926, 627.

## STANDARD METABOLISM

Heat production of a resting animal at standard conditions: Kept post absorptive (see this) between the two critical environmental temperatures (see this). M. K.

## STAPHISAGROINE

An alkaloid of undetermined composition from the seeds of *Delphinium staphisagria*, melting at 276°.

## STAPHYLOCCOCUS

See Microbiology.

## STAR ANISE

Fruit of *Illicium verum* containing tannin, anisic acid, resin, pectin and other constituents, and used as a carminative like anise.

## STARCH

The most important hexosan. It is the source of energy for plants. The starch molecule consists largely of glucosidal linked  $\alpha$ -glucopyranose units, which are coiled back to form a closer unit, and are held in this position by secondary valences. Starch granules probably are composed of a readily water-dispersible  $\alpha$ -amylose (granulose) and a difficultly dispersible phosphorus containing  $\alpha$ -amylose (amylopectin), which are separable.

## STARCH, SOLUBLE

A somewhat hydrolyzed starch showing an increase in reducing power and smaller molecular

weight; used for determination of diastatic power of malt and as indicator for iodine.

# STARCH VALUE

An index of digestibility of raw fodders; the percentage of utilization as compared to the total starch. M. K.

# STARVATION

See Creatine and Creatinine Metabolism.

# STEADY STATE

Dynamic equilibrium; the condition of balance between varying, shifting, and opposing forces, which is especially characteristic of living processes.

# STEAP SIN

Old name for lipase of pancreatic juice.

See Enzymes, Non-Proteolytic.

# STEARIC ACID

A saturated fatty acid,  $\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$ , found in animal and vegetable fats, m.p.  $69-70^\circ$ , b.p.  $383^\circ$ ; used in suppositories, ointments, enteric coatings for bitter drugs.

# STEARIDONIC ACID

An 18 carbon unsaturated fatty acid with four double bonds.

# STEATORRHEA

The appearance of fat in the feces.

# STEFAN'S LAW

In 1886, Stefan propounded the generalization that one half of the latent heat of vaporization of a liquid was expended in pulling a molecule of the liquid into the surface film; the remainder being expended in pulling it out of the surface film into the vapor phase. In 1922, Harkins and Roberts showed, that at best, Stefan's law is only very roughly true.

# STEIGMANN REACTIONS FOR VITAMIN D

With fuchsin-sulfurous acid, solid irradiated ergosterol acquires a violet color.

Heating solid irradiated ergosterol with ammoniacal silver oxide yields a stable silver sol.

Reference: Kolloid-Zeit. 45, 165 (1928).

# STEINLE-KAHLENBERG REACTION FOR CHOLESTEROL

A chloroform solution of antimony trichloride gives a muddy brown precipitate with a dilute cholesterol solution. With excess chloroform, the precipitate dissolves to form a clear purple liquid quickly changing to cobalt-blue on exposure to light.

Reference: J. Biol. Chem. 67, 425 (1926).

# STENOHALINE

A term applied to animals that cannot withstand a material change in external salinity, e.g. spider crab *Maia*; opposite of euryhaline.

# STEPPHIN-UTKIN-LJUBOWZOW METHOD FOR DETERMINING BAYER 205 (Germanin)

The determination in urine, serum and tissues depends upon decomposition of the substance in boiling alkali. The liberated components are coupled with diazo compounds; the resultant colored substances are determined colorimetrically.

Reference: Klin. Wochschr. 1923, 154.

# STERCOBILIN

See Uribilin.

# STERCOBILINOGEN

See Urobilinogen.

## STEROIDS

Steroids comprise a group of isocyclic products of plant and animal origin with a tetracyclic hydromatic ring system, perhydro-cyclopentenophenanthrene (CPP), as common nucleus. This carbon skeleton was correctly formulated, 1932, by Rosenheim and King as consisting of 1 five-membered and 3 six-membered rings, in angular annelation. It carries as sidechains 2 angular methyl groups and in many instances a side chain of 2 to 10 carbon atoms. Hydroxyl and carbonyl groups are the most important functional groups occurring in the cyclic and acyclic portions of the molecule, while a carboxyl group in the acyclic sidechain characterizes the bile acids, an important subdivision. Additional variety is caused by the presence in the cyclic and acyclic portions of double bonds which in the estrogenic hormones are accumulated in one or two rings, giving rise to a benzene or naphthalene system. An immense number of further isomeric possibilities is offered by the steric configuration on 4-10 asymmetric carbon atoms, but, remarkably enough, only a small number of them is realized in natural products. This selectivity of nature plays part in the great stability of the steroid skeleton which survives postmortally all other organic constituents of the animal body, carbohydrates, proteins, and fats, is found as "adipocere" under certain conditions in skeletonized cadavers and has also been linked to the origin of "mineral" oil.

Table I shows animal and plant representatives of steroids arranged according to number of carbon atoms. One principal difference between these two series is the pre-

ponderance of tertiary hydroxyl groups in plant steroids, but of secondary hydroxyl groups in animal steroids. As steroids are mostly of hydrophobic character, nature endeavors to render them water-soluble for various physiological functions by conjugation with hydrophilic groups. This is accomplished in the plant (neutral saponins, cardiac glycosides, and the steroid solanum alkaloids) by glycosidic linkage to hexoses and certain desoxyhexoses, in the animal by conjugation with the amino acids glycine and taurine in the case of the bile acids, with  $H_2SO_4$  in scymmol in shark's bile, and with suberyl arginine in toad poison.

The biogenesis of the steroids is still obscure although the combination of several isoprene units offers a suggestive hypothesis. Experiments with heavy isotope tracers indicate the rapid synthesis from even smaller fragments, but it is undecided whether the general course of synthesis issues from amino acids such as leucine, containing a preformed isoprene skeleton, or from carbohydrate fragments.

Their catabolism in the animal body is obviously of an oxidative nature, first chopping off the side-chain and finally leading to dehydrogenation of the remaining cyclic rump. Whether complete dehydrogenation, leading to polycyclic aromatic hydrocarbons, closely related to the most carcinogenic compounds known, has any bearing on the pathogenesis of spontaneous tumors or is merely a formal coincidence, is doubtful. In any event, the powerful stimulating action of the steroid hormones on the various primary and secondary reproductive tissues seems a generic property

whose specificity is delicately governed by minute structural and steric differences.

Many physiological functions of steroids may be traced to their surface activity. This, in turn, is due to the spatial configuration of the molecule and the polar distribution of hydrophilic and oleophilic groups, which offer themselves to study by the elegant methods of "twodimensional" chemistry in monomolecular layers. This surface activity endows bile acids with emulsifying power for fats in the digestive tract; it gives to cholesterol and its esters the rôle of a mediator between protoplasm and lipid membranes, and contributes to the pharmacologi-

cally valuable properties of the cardiac glycosides and the cytolytic saponins.

Steroid chemistry has greatly stimulated the development of modern methods of structural investigation and organic synthesis (in the hands of Mauthner, Windaus, Wieland, Rosenheim, Jacobs, Heilbron, Ruzicka, Reichstein, Robinson, Fieser, Marker, Bachmann, etc.). (See L. F. Fieser, *The Chemistry of Natural Products Related to Phenanthrene*, New York, 1937. H. Sobotka, *Chemistry of the Steroids*, Baltimore, 1938 with a classified catalog of steroid compounds).

HARRY SOBOTKA,  
Mt. Sinai Hospital, New York.

Number of Carbon Atoms	Animal Steroids	Plant Steroids
29	_____	Phytosterols
28	_____	Ergosterol, calciferol
27	Cholesterol, scymnol	Saponins, Solanum alkaloids
23	Bile acids, toad poison	Scilla glycosides
21	_____	Digitalis and Strophanthus glycosides
24	Hormones of corpus luteum and adrenal cortex	_____
19	Androgenic Hormones	_____
18	Estrogenic Hormones	_____

## STEROLS

Sterids; sometimes refers specifically to those sterids with a hydroxyl group in the structure. Compounds containing the perhydrocyclopentano phenanthrene nucleus.

Found in cholesterol, the saponins, certain hormones, especially the sex hormones, and in various plant and animal tissues.

## STEROLS, TESTS FOR

See Montignie, Rosenheim-Cal-low.

## STEUDEL REACTION FOR NUCLEIC ACID

Treatment of the acid, on a slide, with concentrated nitric acid leads to the formation of doubly refractive crystals of the nitrates of the purine bases. Concentrated hydrochloric acid may also be used.

Reference: Zeit. physiol. Chem. 48, 427 (1906).

# STIGMASTEROL

$C_{20}H_{48}O$ , m.p.  $170^{\circ}$ , forms a hydrate, a sterol of many plants, e.g. soya bean, calabar bean and other legumes.

# STILBESTROL

Stilboestrol; 4:4'-dihydroxy-alpha-beta-diethyl-stilbene, a synthetic estrogenic substance which can be taken orally and is more potent than estrone and can be used for the same menstrual disorders, e.g. amonrrhea, dysmenorrhea.

# STILBOESTROL

See Stilbestrol.

# STIMULUS

Any agent, act, or influence that produces functional or trophic reaction in an irritable tissue.

See Nervous System.

# STINKWEED

See Stramonium.

# STOELTZNER TEST FOR VITAMIN D

A 1% solution of the vitamin in olive oil is treated with phosphorus pentoxide yielding a reddish-brown color which develops outward from the pentoxide and gradually darkens until almost black. The reaction is also given by cod liver oil.

Reference: Münch. med. Wochschr. 75, 1584 (1928).

# STOMACH

See Gastro-Enterology.

# STRAMID

See Sulfanilamide.

# STRAMONIUM

Thorn apple, Jimson weed; stinkweed; Devil's apple; dried leaves of *Datura Stramonium* containing the alkaloid hyoscyamine; used

for relief of asthma and acts through the simultaneous presence of atropine and scopolamine; narcotic, antispasmodic, sedative; average dose 75 mgm.

# STRAUB FLAVOPROTEIN (HEART)

Coenzyme factor; diaphorase; a heart flavoprotein enzyme, m.w. about 70,000, absorption bands at 274,359 and 451 mμ, yellow-green; prosthetic group is flavinadenine dinucleotide; participates in reoxidizing reduced coenzyme I (dihydrocoenzyme I) itself forming a leuco-flavoprotein which reduces a carrier, the reduced form of which finally reacts with molecular oxygen; universally distributed in animal tissues.

# STREAMING POTENTIAL

The potential difference induced between the ends of a capillary when a liquid is forced through it.

# STREAMING, PROTOPLASMIC

See Protoplasm.

# STREPTOCID

See Sulfanilamide.

# STREPTOCOCCUS

See Microbiology.

# STROPHANTHIDIN

$C_{23}H_{32}O_6$ , m.p.  $169-170^{\circ}$  with  $2H_2O$ , a cardiac aglucone of strophanthin glycosides, such as strophanthin, scillaren and digitoxin.

# G-STROPHANTHIN

See Ouabain.

# STROPHANTHIN

The cardiac glycoside or mixture of glycosides of strophanthus; used like digitalis; dose 0.25-0.50 mgm.

# STROPHANTHIN TEST

See Baljet.



## STROPHANTHUS

Dried ripe seeds of *Strophanthus kombé* containing the cardiac glycoside strophanthin, kombic acid, choline and trigonelline, a heart tonic.

## STROUP TEST FOR DIFFERENTIATING CAFFEINE AND THEOBROMINE

One drop of a 1:20 solution of potassium dichromate in sulfuric acid is added to the triturated sample in a porcelain dish. Caffeine produces a light blue-green color; theobromine gives a dark purple color, changing gradually to purple-green, olive-green and blue-green.

Reference: *Am. J. Pharm.* 93, 598 (1919).

## STRUCTURE, PROTOPLASMIC

See Protoplasm.

## STRYCHNINE

$C_{21}H_{22}O_2N_2$ , m.p. 286-288°, alkaloid of *nux vomica*, etc., raises blood pressure, heart stimulant, promotes appetite; dose 1.5 mgm. See Toxicology.

## STRYCHNINE TEST

See Malaquin.

## STURINE

A protamine of the testicles of the sturgeon.

## STYLOPENE

An alkaloid,  $C_{16}H_{17}O_4N$ , from the root of *stylophoron diphylum* and melting at 202°.

## STYRACITOL

1:5-anhydrosorbitol, m.p. 157°; found in the peel of *Styrax obassia*.

## SUBERIN

Cork material of cell walls of higher plants.

## SUBMICRONS

In the Siedentopf and Zsigmondy classification of particle size, those particles visible in the ultramicroscope. Ultramicros.

See Amicrons.

## SUBSTANCE 248

See Toxisterol.

## SUCCINIC ACID

Amber acid, ethylenesuccinic acid;  $HOOC-CH_2CH_2-COOH$ ; sp.gr. 1.56; m.p. 185-187°; b.p. 235° with partial conversion to anhydride; used in mfg. of dyes, perfumes, lacquers; salts are used medicinally.

## SUCCINIC ACID TEST

See Neuberg.

## SUCCINIC CYCLE

The theory of Szent-Györgyi and coworkers to explain the sustaining of oxygen uptake of minced muscle by succinate, fumarate, malate and oxaloacetate which are interconvertible and act as intermediators between metabolites and cytochrome-oxygen; triosephosphate is the chief metabolite concerned and is oxidized by oxaloacetate.

## SUCCINIC DEHYDROGENASE

A cytochrome-reducing dehydrogenase of heart muscle, etc., which catalyzes the oxidation of succinic acid to fumaric acid, especially in presence of cytochrome c.

## SUCCUS ENTERICUS

Alkaline digestive juices produced by Brunner's and Lieberkuhn's glands; most abundant in the duodenum and in lesser amounts in the rest of the small intestine. It contains proteolytic enzymes, phosphatases, carbohydrases, and enterokinase. (All of which see.)

**SUCRASE**

A carbohydrase of the intestine and of yeast, that hydrolyzes sucrose to fructose and glucose. Optimum pH about 4.5.

See Invertase, Enzymes, Non-Proteolytic.

**SUCROSE**

Cane sugar, beet sugar. It is the most important non-reducing disaccharide. Obtained from the sugar cane or the sugar beet, as the sugar of commerce. It is  $\alpha$ -glucopyranose-1- $\beta$ -fructofuranoside.

See Disaccharides.

**SUCROSE TESTS**

See Raybin, Seliwanoff, Wagenaar.

**SUDORIFIC**

Promoting the flow of sweat.

**SUGAHARA REACTION FOR LEVULOSE**

A mixture of 1 cc. of sugar solution, 2 cc. of 0.7N sulfuric acid and 10% sodium tungstate is treated with calcium oxide until faintly alkaline. A green precipitate forms, with large amounts of levulose the solution also turns green. The test gives a sharp differentiation between glucose and levulose.

Reference: J. Biochem. (Japan) 22, 85 (1935).

**SUGAR, BLOOD**

See Blood Sugar.

**SUGAR, BLOOD, TESTS FOR**

See Glucose Tests.

**SUGARS, REDUCING, TESTS FOR**

See Benedict Reagents, Bose, Dominikiewicz, Pavolini.

**SUIDA REACTION FOR ASPARTIC ACID**

Basic dyes, like crystal violet, Nile blue and safranin precipitate aqueous solutions of the hydrochloride of the acid.

Reference: Zeit. physiol. Chem. 1907, 174.

**SULFADIAZINE**

See Chemotherapy.

**SULFAMIDYL**

See Sulfanilamide.

See Chemotherapy.

**SULFANILAMIDE**

Sulfonamide-P; p-aminobenzene-sulfonamide; m.p. 164.5-166.5°; a bacteriostatic agent for bacterial infection, especially of streptococci and meningococci; dose, 1 gm. daily for each 20 lb. body weight up to 100 lbs.

**SULFANILAMIDE TESTS**

See Schmidt, Scudi (Micro).

**SULFANILID TEST**

See Denigès.

**SULFAPYRIDINE**

Dagenan; 2-sulfanilyl aminopyridine; m.p. 190-193°; used for pneumonia and gonorrhea.

See Chemotherapy.

See Enzymes, Non-Proteolytic.

**SULFATASE**

A specific enzyme which splits organic sulfates (but not chondroitin sulfuric acid).

**SULFATHIAZOLE**

See Chemotherapy.

**SULFATIDES**

Compounds of sulfur with lipids, found in brain and nervous tissue. P may be absent.

**SULFHEMOGLOBIN**

Results from the ingestion of acetanilide and sulfanilic acid deriva-

tives; may be made by the action of hydrogen peroxide and a sulfide on reduced hemoglobin.

## SULFHYDRYL

The grouping of sulfur and hydrogen as SH, found in amino acids, proteins, oxidation-reduction systems.

## SULFHYDRYL REACTIONS

See Unna-Golodetz, Zimmet.

## SULFOHEME

A hypothetical analogue of oxyheme considered as a component of sulfhemoglobin.

## SULFONAMIDE DRUGS

See Chemotherapy.

## SULFONAMIDE P

See Sulfanilamide.

## SULFUR BACTERIA

(VAN NIEL)

Facultative autotrophants which are strict anaerobes capable of oxidizing sulfur or sulfur compounds.

## SULFURIC ACID

See Detoxication.

## SULFUR IN ORGANIC

## COMPOUNDS, TEST FOR

See Grote.

## SULLIVAN REACTION FOR

## GUANIDINE

One-half mg. of base in 1 cc. of aqueous solution is treated with 1 cc. freshly prepared 1% solution of sodium 1,2-naphthoquinone-4-sulfonate and 0.3-0.5 cc. of N sodium hydroxide and placed in a boiling water bath for 1-2 minutes. After cooling, 0.3 cc. of 25% solution of urea are added, acidified with 1 cc. concentrated hydrochloric acid, mixed and 1 cc. concentrated nitric acid added. A distinctly red solution is obtained.

Reference: Proc. Soc. Exptl. Biol. Med. 33, 106 (1935).

## SULLIVAN TESTS FOR CYSTINE AND CYSTEINE

I. Cystine—Five cc. of test solution (0.1N with respect to hydrochloric acid) is treated with 1 cc. freshly prepared 1% sodium cyanide solution, shaken, and treated with 1 cc. freshly prepared aqueous 0.5% solution of sodium-1,2-naphthoquinone-4-sulfonate. After shaking 5-10 seconds, 5 cc. of 10-20% solution of anhydrous sodium sulfite in 0.5N sodium hydroxide are added. After mixing and standing at 20° for 10 minutes, a reddish-brown color appears. The addition of 1 cc. of 2% sodium hyposulfite solution in 0.5N sodium hydroxide changes the reddish color to a purer red.

II. Cystine—A mixture of 5 cc. test solution and 2 cc. freshly prepared aqueous 5% sodium cyanide solution is allowed to stand for 10 minutes. One cc. of 0.5% solution of sodium 1,2-naphthoquinone-4-sulfonate is added and the mixture shaken 10 minutes. 5 cc. of 10% solution of anhydrous sodium sulfite in 0.5N sodium hydroxide are added, mixed and allowed to stand 30 minutes; 2 cc. 5N sodium hydroxide and 1 cc. of 2% sodium hyposulfite in 0.5N sodium hydroxide are added. Color reactions as given above are given if at least 100 p.p.m. of cystine are present. The test may be used for the colorimetric estimation of the compounds and is not given by glutathione and many other compounds.

Reference: J. Biol. Chem. 59, 1 (1924). U.S. Pub. Health Repts. suppl. No. 78 (1929); 46, 390 (1931).

## SUMACH

Dried ripe fruit of *Rhus glabra* containing tannin, etc., and used as astringent. (The bark is utilized also for the same purpose.)

## SUMNER REAGENTS AND TESTS FOR GLUCOSE IN URINE

I. In normal and diabetic urine sugar reduces 4,6-dinitroguaiacol to intensely colored 4-nitro-6-aminoguaiacol when heated in the presence of sodium carbonate.

II. Ten grams crystalline phenol are mixed with 22 cc. 10% sodium hydroxide and diluted to 100 cc. with water. 6.9 gm. of sodium bisulfite are added to 69 cc. of the phenol solution, followed by a solution containing 300 cc. 45% sodium hydroxide, 255 gm. Rochelle salts and 800 cc. of 1% 3,5-dinitrosalicylic acid. After mixing, the solution is kept lightly stoppered in a well-filled bottle.

III. Reagent—Solution of 2 gm. 3,5-dinitrosalicylic acid in 100 cc. 2% sodium carbonate solution. One cc. urine, 1 cc. reagent and 2 cc. 1.5% sodium hydroxide are heated in a boiling water bath for 5 minutes. Cool and compare the red color with a similarly treated mixture of 1 mg. glucose in 1 cc. water and 1 cc. reagent. Reference: J. Biol. Chem. 46, xxi (1921); 47, 5 (1921). Proc. Soc. Exptl. Biol. Med. 20, 96 (1922).

## SUPERMETABOLISM

A term suggested by Murlin to include the effects of all the known factors which cause a rate of heat production higher than basal in normal subjects; includes the specific dynamic action of protein (S.D.A.) and the effects of temperature, as in hibernation. M. K.

## SUPRANEPHRINE

A commercial preparation of 1-epinephrine hydrochloride.

## SUPRARENAL

Adrenal.

## SUPRARENALIN

A commercial preparation of 1-epinephrine hydrochloride.

## SUPRARENIN(E)

See Epinephrine.

## SUPRATEROL I

A sterol derivative m.p. 104° C., obtained by the ultraviolet irradiation of calciferol, or the prolonged ultraviolet irradiation of ergosterol. It contains 4 rings, and three unconjugated double bonds. See Vitamin D.

## SUPRATEROL II

A product obtained by the ultraviolet irradiation of calciferol, m.p. 110°.

## SWAMINATHAN TEST FOR NICOTINIC ACID IN FOODSTUFFS

A hot, aqueous extract of the foodstuff is treated with lead acetate solution to precipitate the proteins, excess lead is removed with sulfuric acid, the pH adjusted to 10 and any color removed with charcoal. The clear, colorless filtrate is adjusted to pH 7.5 and made up to volume. An aliquot is diluted with water to 20-30 cc. in a 100 cc. separatory funnel, 4 cc. freshly prepared cyanogen bromide solution added, shaken and allowed to stand for ½ hour. The yellowish-green color is extracted three times with 10 cc., 5 cc., and 5 cc. portions of purified amyl alcohol and compared with a known nicotinic acid standard.

0.01 mg. of the acid is easily detected, and definite gradations

of color are obtained for increments of 0.01 mg. up to 0.1 mg. nicotinic acid.

Reference: Nature 141, 830 (1938).

## SYMBIONT

See Symbiosis.

## SYMBIOSIS

The living together or close association of two dissimilar organisms to the advantage of both; each organism known as a symbiont.

## SYMPATHECTOMY

See Wound Healing.

## SYMPATHETIC SYSTEM

See Neurophysiology.

## SYMPATHETIC SYSTEMS, DRUG EFFECTS ON

See Pharmacology.

## SYMPATHOMIMETIC

Stimulating the sympathetic nerves, e.g. as by the action of epinephrine, tyramine and epinene.

## SYMPATHIN

A compound localized in the nerves and acting in the transmission process; may be adrenaline; acts with acetylcholine (q.v.). Possibly adrenaline combines with two cellular substances to form Sympathin E and Sympathin I.

See Neurophysiology.

## SYNAPSE

The anatomical relation of one nerve cell to another; the region of contact between processes of two adjacent neurons, forming the place where a nervous impulse is transmitted from one neuron to another.

## SYNERGISM

(1) The joint action of drugs whose combined effect is greater than the sum of the individual effects; (2) muscle coordination.

## SYNDROME

A complex of symptoms; a set of symptoms which occur together; the sum of signs of any morbid state.

## SYNERESIS

The loss of dispersions medium by a colloidal sol.

## SYNOVIAL FLUID

A clear, thick, alkaline liquid found bathing tendons, joints and bursae; acts as a cushioning and lubricating medium; similar, in most respects, to plasma composition.

## SYNTHALIN

Decamethylene-diguanidine dihydrochloride; m.p. 193°; has insulin-like effect, but operates merely by being toxic to the nervous system.

See also Insulin.

## SYNTHESIS, PROTEIN

See Autolysis.

## SYNTONIN

Acid myosin; a metaprotein resembling various albuminates.

## SYPHILIS

A chronic, infectious disease due to *Treponema pallidum* or *Spirochaeta pallida*. It may be (1) acquired or (2) prenatal. Infection may be spread through any abrasion. Three stages are described: primary, secondary and tertiary. In the first stage a chancre appears at the site of infection which, however, is systemic. It is an immunity reaction which becomes prevalent in the secondary stage. In the tertiary form the lesion is the gumma but every kind of symptom of other disease may be involved also. Many laboratory tests have been devised for diagnosis, of which the most famous is the Wassermann test

(which see) which is a complement fixation test. Flocculation tests also have been used (Kahn, Kline, Eagle) as well as agglutination (Hinton).

The spectacular use of arsphenamine, Ehrlich's 606, and of neoarsphenamine and other arsenicals, in this disease gave a strong impetus to the modern science of chemotherapy. Bismuth and mercury are supplementary to such therapy. A popular compound for use in neurosyphilis is tryparsamide or sodium-N-phenylglycinamide-p-arsonate.

#### SYRINGIN

5-methoxy coniferin, found in *Syringa* species,  $C_{17}H_{24}O_9H_2O$ , m.p. 192°. A glucoside yielding

syringenin and glucose on hydrolysis.

#### SYSTEM, AUTONOMIC

See Neurophysiology.

#### SYSTOLE

Contraction of an organ, e.g. the heart.

#### SZENT-GYÖRGYI REACTION FOR ASCORBIC ACID

A slightly alkaline 1% solution of the acid is mixed with ferrous sulfate solution and exposed to the air. A dark violet color, visible even after 100-fold dilution, forms rapidly. Reduction with sodium hyposulfite destroys the color, exposure to air restores it.

Reference: Zeit. physiol. Chem. 1934, 168.



## T

### TABACIN

A glucoside from the leaves of Kentucky tobacco, converted by KOH to nicotine; toxic, paralyzes heart and respiration; lethal dose 80 mgm. per kilo.

### TACHYPHYLAXIS

The appearance of decreased effects on repeated injection of a substance.

### TACHYSTEROL

An unstable, non-anti-rachitic, toxic, irradiation product of ergosterol. On further irradiation yields calciferol. Contains three rings and four conjugated double bonds. See Vitamin D.

### TADPOLE METAMORPHOSIS

See Autolysis.

### TAKA-DIASTASE

An enzyme preparation obtained by growing the fungus *Aspergillus oryzae* on bran, leaching the mass of culture with water, and precipitating with alcohol; a mixture of enzymes, largely used for its diastatic properties; also known as koji; whitish-yellow, hygroscopic powder, converts over 300 times its weight of starch into maltose.

### TAKEUCHI REAGENT FOR UREA

An aqueous soybean extract

(containing the ferment urease) can convert urea into ammonia at ordinary temperatures. The amount of urea may be determined by titrating the resulting ammonium carbonate. The urea content of urine, blood serum and cerebrospinal fluid may be determined with this reagent.

Reference: J. Coll. Agr. Tokyo Imp. Univ. 1909, 1. J. Biol. Chem. 14, 283; 15, 487, 495. Deut. med. Wochschr. 1914, 430; 1914, 1219.

### TAMARIND

Partially dried ripe fruit of *tamarindus indica* preserved in sugar or syrup and used as laxative, refrigerant.

### TAMPICIN

A glucoside,  $C_{34}H_{54}O_{14}$ ; m.p.  $130^{\circ}$ ; a constituent of tampico resin and similar pharmacol. to convolvulin.

### TANACETIN

An amaroid from seed, herb, and flowers of *Tanacetum vulgare*.

### TANGHININ

$C_{27}H_{40}O_8$ ; from the seed of *Tanghinia madagascariensis* Pet., Apocynaceae; a heart poison closely resembling strophanthin and ouabain but differing in its spastic action.

## TANNASE

An esterase which hydrolyzes only esters the acid component of which has at least two phenolic hydroxy groups, neither of the hydroxyls being ortho to the carboxyl of the acid. Found in mould fungi.

See Enzymes, Non-Proteolytic.

## TANNIC ACID

Tannin; gallotannic acid; a glycoside of gallic acid;  $C_{76}H_{52}O_{46}$ ; used as styptic and in the treatment of burns.

## TANNIN

See Tannic Acid.

## TANNINS

A group of naturally occurring complex glycosides found usually in tree barks. Vary in complexity from Turkish tannin, which is a glycoside containing one molecule of glucose and five of gallic acid to more complex ones as Chinese tannin, which contains 10 molecules of gallic acid to one glucose. Form colloids with hot water; inks with iron salts; insoluble precipitates with gelatin; precipitated by alkaloids and proteins; astringent.

## TANNINS,

### CLASSIFICATION OF

Freudenberg, K., Die Chemie der natuerlichen Gerbstoffe, classifies tannins as follows:

1. Condensed tannins—
  - a. Catechin tannins (asacatechin, isoasacatechin, gambier catechin).
2. Hydrolyzable tannins.—
  - a. Gallotannins.
  - b. Elagitannins.
  - c. Caffetannins.
3. Unclassified tannins.

## TANNOFORM

Tannin-formaldehyde, m.p.  $230^{\circ}$ ; a condensation product of formaldehyde and tannic acid, used as an intestinal antiseptic.

## TANRET REACTION FOR ERGOTININE

When a trace of ergotinine is treated with a few drops of ethyl acetate and concentrated sulfuric acid, a yellow-red color is obtained which changes rapidly to violet and blue; the color is not altered by water.

Reference: Ann. chim. phys. 17, 493.

## TAPEWORM

See Worms, Intestinal.

## TARAXANTHIN

A carotenoid,  $C_{40}H_{56}O_4$ , m.p.  $185^{\circ}$ , whose esters are present in dandelion petals; isomer of violaxanthin.

## TARGET GLANDS

The glands controlled by the hormones of the pituitary.

## TARTAR

A precipitate coating teeth, principally calcium phosphate, sulfomucin and cellular debris.

## TARTARIC ACID

Dextrotartaric acid, dihydroxy-succinic acid;  $C_4H_4O_6$ ; a dihydroxy, dicarboxylic acid occurring in many fruits and in mfg. of wine; m.p.  $168-170^{\circ}$ ; sp. gr., 1.76; used as refrigerant, in preparing effervescent powders; industrially in baking powders, coloring and dyeing, as reagent in anal. chemistry.

## TARTARIC ACID TEST

See Wagenaar.

# TAUBER REACTION FOR VITAMIN B<sub>1</sub>

Several mg. of vitamin and 5 mg. p-dimethylaminobenzaldehyde are mixed in a small crucible and evaporated with 0.1 cc. glacial acetic acid. After cooling, the addition of 1 cc. glacial acetic acid immediately produces an intense brick-red color. Proteins and amino-acids interfere.

Reference: Science 86, 594 (1937).

# TAUBER TEST FOR ASCORBIC ACID IN PLANTS, ETC.

A few gm. of vegetable or organic tissue is macerated with 2 or 3 times as much hot 8% acetic acid for a few minutes. A drop of the liquid is placed on a double filter paper (the upper one for filtration, the lower for the test). One drop of a solution of 1 gm. ferric sulfate in 80 cc. boiling water and 18 cc. 85% phosphoric acid is placed on the lower filter paper and 1% potassium permanganate solution added until a faint pink color results. A blue color develops in 1/2 minute in the presence of 0.003 mg. vitamin in 0.5 cc. solution.

Reference: Mikrochemie 17, 111 (1935).

# TAUBER TEST FOR PENTOSE

Reagent—1 gm. benzidine in 25 cc. glacial acetic acid. This is good for 4 days. One drop of test solution (containing 0.05 mg. or more of pentose) is boiled vigorously with 0.5 cc. of reagent and cooled; a very stable cherry-red color is obtained. Glucose, fructose or galactose give yellow to brown colors.

Reference: Mikrochemie 17, 111 Med. 37, 600 (1937).

# TAURINE

Aminoethylsulphonic acid, combined with cholic acid forms the bile acid, taurocholic acid; originates from cystine in the liver.

# TAUROCHOLIC ACID

C<sub>26</sub>H<sub>45</sub>O<sub>2</sub>NS; m.p. about 125°; cholaic acid; cholytaurine; occurs in bile as Na salt; hydrolyzes to taurine and cholic acid.

# TAXICATIN

A glucoside from leaves of *taxus baccata* melting at 164-165°.

# TAXINE

C<sub>37</sub>H<sub>51</sub>O<sub>10</sub>N; alkaloid from needles and seed of *Taxus baccata*, m.p. 121-124°, an abortive and paralyzant.

# TAXIS

See Tropism.

# TAXONOMY

The study of the laws and principles of classification.

See Protoplasm.

# TEARS

See Eye, Biochemistry of.

# TECTORIDIN

A glucoside from the rhizome of *Iris tectorum*.

# TEETH, BIOCHEMISTRY OF

In order to understand the biochemistry of teeth a brief discussion of their development and histological structure is necessary.

The teeth are highly specialized cutaneous tissues. They consist of a calcified enamel layer covering the crown of a somewhat less calcified dentin, which in turn surrounds the pulp. The pulp is supplied with blood vessels and nerves. Supporting the teeth in the oral cavity and thereby giving them functional significance are the periodontal tissues (cementum, periodontal membrane, alveolar bone, and gingiva). The cementum covers the root dentin, and the tooth rests in its socket

in the alveolar bone. The periodontal membrane lies between the cementum and the alveolar bone. Gingiva, or gum tissue, surrounds the alveolar bone and forms a collar through which the tooth projects into the oral cavity.

Formation of enamel and dentin by the ameloblasts (enamel forming cells) and odontoblasts (dentin forming cells) begins at the dentino-enamel junction. The ameloblasts lay down an organic enamel matrix as they recede outward from the dentino-enamel junction while the odontoblasts lay down an organic dentin matrix and recede inward from the junction thus constricting the pulp cavity. Following the formation of the initial portions of these matrices calcification takes place and proceeds in both directions from the dentino-enamel junction. The enamel and dentin are formed in definite incremental layers 16 micra in width.<sup>1</sup> This 16 micra rhythm has been found to take place in man approximately every 4 days.<sup>2</sup> The process of calcification of each increment of enamel is completed about 3 months after the initial deposition of the organic matrix by the ameloblasts.<sup>3</sup> After eruption of the tooth into the oral cavity the ameloblasts are worn away and thus the enamel is incapable of further growth or regeneration. Since the odontoblasts are still present and functioning after the eruption of the tooth, dentin can continue to grow under pathological conditions. This secondary growth further constricts the pulp cavity.

During calcification of the enamel an inorganic calcium salt (primarily the phosphate) is deposited in, and largely replaces, the organic matrix so that in fully calcified enamel the

organic portion amounts only to about 3 per cent of the total. In fully calcified dentin, on the other hand, the organic portion makes up some 25 per cent of the whole.

#### Methods of Preparing Teeth for Analysis

Since the biochemistry of teeth is primarily concerned with the inorganic phases of enamel and of dentin the following methods are commonly employed in obtaining these fractions.

A large portion of the enamel layer may be mechanically removed from the surface of the crown with the aid of a dental drill, and similarly the dentin can be obtained from the inside of the tooth. These two fractions can then be treated by one of the methods listed below to obtain the inorganic phases when desired.

A second and much better method of separating enamel and dentin makes use of the different specific gravities of the two.<sup>4</sup> The teeth are first cracked into several pieces, the pulps removed and the pieces extracted with a 50-50 alcohol-ether mixture in a Soxhlet extractor to remove any lipids. The lipid-free pieces are pulverized to pass through a 100-mesh screen and these powdered particles of enamel and dentin are suspended in a bromoform-acetone mixture of specific gravity 2.7. The enamel particles, most of which have a specific gravity between 2.89 and 3.00, will sink in this mixture, whereas the dentin and cementum particles with specific gravities of 2.14 and 2.03 respectively will float. The process of separation is facilitated by placing the powdered sample in a removable open cylinder contained in a centrifuge tube.<sup>5</sup> The

enamel particles are rapidly centrifuged through the cylinder and collect in the bottom of the centrifuge tube while the dentin and cementum particles float on the surface of the bromoform-acetone mixture in the cylinder and can be removed with the cylinder. The dentin and cementum particles can subsequently be separated by employing a bromoform-acetone mixture of specific gravity 2.08.

These pure samples of enamel and dentin may now be analyzed as they are, or the organic fractions may be removed and analyses made on the inorganic residues. Ashing in a muffle furnace at 600°-700° C. will suffice to remove all organic matter, or the organic matter may be leached out by a boiling solution of KOH in ethylene glycol.<sup>6</sup>

#### Chemical Methods of Analysis of Enamel and Dentin

The three elements most commonly analyzed for in enamel and dentin are calcium, phosphorus and fluorine.

A convenient and frequently employed method for calcium analysis is the micro titration method which has been applied to blood.<sup>7</sup> In this procedure the calcium is precipitated as the oxalate at pH 5.0. The calcium oxalate is then washed, dis-

solved in hot 1 normal H<sub>2</sub>SO<sub>4</sub> and the resulting oxalic acid is titrated with potassium permanganate.

Phosphorus can be rapidly and accurately determined by the colorimetric method of Fiske and Subbarow.<sup>8</sup> The color is developed by adding an aminonaphtholsulfonic acid reagent to an acid solution containing inorganic phosphate and ammonium molybdate and can be read with a Du Boscq or a photoelectric colorimeter. As little as 5 to 10 micrograms of phosphorus can be determined by this method.

The principle of the micro determination of fluorine<sup>9</sup> involves the titration of hydrofluosilicic acid in a buffer at pH 2.8 with a standard thorium nitrate solution. The end point is determined by the lake which is formed when an excess of thorium ions react with the sodium alizarine sulfonate used as an indicator. As little as one microgram of fluorine can be determined.

#### The Composition of Enamel and Dentin

The inorganic phase of enamel has been variously reported to make up between 95 and 97.5 per cent of whole enamel while for dentin it represents only 71 to 75 per cent. Composition of whole, sound enamel and dentin with respect to the major constituents is as follows:

#### PERCENTAGE COMPOSITION ± STANDARD DEVIATION

	Enamel	Dentin
Calcium <sup>10</sup>	35.41±0.963	26.18±0.342
Phosphorus <sup>10</sup>	17.45±0.513	12.74±0.482
Magnesium <sup>10</sup>	0.30±0.054	0.83±0.083
Carbon Dioxide <sup>10</sup>	3.00±0.249	3.57±0.103
Nitrogen <sup>10</sup>		3.36±0.145
Sodium <sup>11</sup>	0.7*	
Potassium <sup>12</sup>	0.3	<0.3
Fluorine <sup>13</sup>	0.0111±0.00203	0.0169†
Iron <sup>14</sup>	0.0008	

\*This determination was made on the alcohol-KOH residue of enamel.

†Sample prepared by pooling 50 mg. quantities from each of 26 teeth.

In addition to the above mentioned constituents enamel and dentin have been found, on spectrographic examination, to contain traces of the following elements: aluminum, barium, boron, chromium, copper, lead, manganese nickel, silicon, silver, strontium, tin, titanium, vanadium, and zinc.<sup>15, 16</sup>

### Crystal Structure

Several investigations<sup>17-23</sup> have confirmed the fact, which had previously been recognized, that the powder X-ray diffraction patterns of the mineral of bone, enamel and dentin are very similar to those of the mineral apatites and that the differences in detail of the patterns are to be accounted for, in some degree, by variations in grain size of the crystallites. Actually the diffraction patterns and lattice constants of enamel and dentin more closely match those of hydroxyapatite than those of other members of the apatite group of minerals. It appears certain, therefore, that the fundamental crystal structure, of at least the predominant part of the mineral phase of calcified tissues, is that of an apatite. The apatites are a series of isomorphous minerals of wide distribution and variable composition. Hydroxyapatite has the formula  $\text{Ca}_{10}(\text{OH})_2(\text{PO}_4)_6$ . A variety of substitutions are possible without disrupting the apatite structure. For example, chlorine or fluorine can replace the hydroxyl groups; and magnesium, sodium or potassium can replace some of the calcium atoms. Formerly it was assumed that the carbonate found in many apatites could occupy one of the hydroxyl positions in the crystal lattice but this possibility has now been excluded for structural reasons.<sup>24</sup> One hypothesis<sup>24</sup> as to the position occupied

by carbon in these crystals assumes that to a limited extent carbon can replace either calcium or phosphorus to give the following formula:  $(\text{OH})_2 \text{Ca}_8 [(\text{P,C})\text{O}_4]_6 (\text{Ca,C})_4$ . On this hypothesis the degree of substitution of carbon in the crystal structure is higher in the case of dentin than in that of enamel. Another group of workers<sup>21-23, 25</sup> prefer the view that carbonate apatites do not occur in calcified tissues, and that the sole apatite present in these substances is hydroxyapatite with "occluded, adsorbed, or interstitially crystallized carbonates."

The average size of enamel crystallites in 0.27 micra whereas dentin crystallites are about one-tenth this size.<sup>22</sup>

### Special Methods of Study

**X-ray Absorption Method:**<sup>26</sup> Roentgenograms of tooth slabs will depict the degree of calcification at various points in the enamel and dentin. Any points or areas of abnormal calcification can be detected when the plate is read on a densitometer. The densitometer employs a photoelectric cell and a galvanometer which accurately measure the intensity of light transmitted through various portions of the film. The more intense the light transmitted by a portion of the film, the more opaque, and therefore, the more highly calcified was that portion of the tooth slab.

**Radioactive Isotope Method:** A much debated question in the field of the biochemistry of teeth has been concerned with the ability of erupted teeth to exhibit, or be influenced by metabolic processes. The advent of such radioactive isotopes as those of calcium, phosphorus, fluorine and sodium, has opened a



new approach not only to this question but also to the question of the pre-eruption metabolism of teeth. The isotopes may be administered orally or by any parenteral route and the degree of deposit, exchange, or uptake of radioactive atoms may be measured with a Geiger-Müller counter.<sup>27</sup> This approach has led to many interesting findings which will be discussed later.

**Dietary Methods.** The effect of nutritional factors on the development of teeth and on the preservation of their integrity can be studied by dietary methods. The rat is an extremely useful laboratory animal for such experiments because of the fact that the incisor teeth of the rat are continuously erupting teeth while the rat molars are mature erupted teeth. Such nutritional factors as the vitamins A, C, and D and the elements calcium, magnesium, phosphorus and fluorine have been extensively studied. It may be mentioned here that whereas the effect of dietary deficiencies on developing bone are qualitatively and quantitatively different from those produced in the completely formed skeleton, mature teeth, by contrast, appear to be almost, if not entirely, removed from the direct influence of nutrition. In several instances even developing teeth appear to be less liable to alteration by metabolic influences than forming bone.

**Experimental Dental Caries in Rats:** The ability of teeth to resist dental caries, under a variety of experimental conditions, can be studied in the rat. The molar teeth of rats are sufficiently similar to human molars so that at least some conclusions of practical importance can be drawn from such animal

experimentation. Caries may be produced in a rat molars by employing a diet containing coarse cereal particles. A convenient diet is as follows: 60 parts of coarse, yellow cornmeal; 24 parts of skim milk powder; 12 parts of linseed meal; 3 parts of alfalfa meal; and 1 part of sodium chloride. The animals are fed this diet for 100 days at the end of which time the number of carious lesions are determined. Several methods are available for scoring dental caries. One of these which has been found useful is the method of Gomori.<sup>28</sup>

#### Metabolism

**Vitamin A:** Severe total dietary deficiencies of vitamin A produce, in developing teeth, characteristic abnormalities of structure and growth. The primary dental disturbance in vitamin A deficiency is apparently on the developing enamel.<sup>29</sup> This effect is, then, an example of the specific requirement for this vitamin by epithelial tissues and by those tissues derived from epithelium. Although an early effect of vitamin A deficiency is a result of failure of ameloblastic activity, which may result in enamel agenesis or hypoplasia, a prominent end-result is seen in a disorganized structure of the dentin.<sup>30</sup> The differentiation of odontoblasts from pulpal cells fails in the absence of normally functioning odontogenic epithelium, which failure results in marked disturbances of the growth of dentin. That these effects of vitamin A deficiency are largely confined to developing teeth is nicely brought out by experiments in which rats are placed on the deficient diet at weaning when calcification of the molar teeth is nearly complete. In these experiments marked disturbances of the

continuously erupting incisors are evident but few, if any, disturbances are noted in the molars.

**Vitamin C:** Another vitamin required for normal tooth formation is vitamin C. The most prominent dental effects of ascorbic acid deficiency are produced in the dentin<sup>31</sup> with only minor, and possibly secondary, effects in the enamel. Normal dentin during its formation has a higher requirement for vitamin C than do many other tissues, and for this reason abnormalities in the dentin may be produced in the absence of obvious clinical signs of scurvy. As is well known, the gums and other investing tissues of the teeth of mature animals may be adversely affected in susceptible animals by a deficient supply of vitamin C. However, like vitamin A, there is no indication that ascorbic acid is required for the preservation and integrity of fully formed enamel and dentin.

**Vitamin D, Calcium and Phosphorus:** On diets adequate in calcium and phosphorus but deficient in vitamin D, only slight local irregularities in enamel and dentin are observed in developing teeth. However when diets are deficient in either calcium or phosphorus as well as vitamin D more marked abnormalities occur.<sup>32-34</sup>

Although some degree of enamel hypoplasia, that is, surface irregularities in the enamel, occurs in animals fed on vitamin D-free diets which are also deficient in calcium or phosphorus, the most pronounced effects are on developing dentin. On a rachitogenic diet which is low in phosphorus, free of vitamin D, but normal with respect to calcium, the band of predentin increases in width. Predentin is the dentin or-

ganic phase which has not yet been calcified. A single curative dose of vitamin D will, after a delay of 4 or 5 days, bring about normal calcification in the predentin laid down after the vitamin was administered. However, the predentin laid down during the period of vitamin deficiency remains essentially uncalcified.

Failure of predentin to calcify also occurs on diets which are low in calcium and vitamin D but adequate in phosphorus. Again, vitamin D therapy restores the calcification of subsequently formed predentin almost, if not completely, to normal. It should be emphasized again that, like vitamins A and C, deficiencies of vitamin D, of calcium, or of phosphorus exert practically no influence on preformed enamel and dentin. However, such nutritional deficiencies do produce alterations in the alveolar bone and other investing tissues and consequently do impair the function of fully formed teeth.

It must not be concluded from the above statements that fully formed enamel and dentin are incapable of interaction with substances present in the plasma and saliva. Experiments carried out with the aid of radioactive calcium<sup>35, 36</sup> and radioactive phosphorus<sup>37-40</sup> have amply demonstrated that both enamel and dentin of fully formed teeth can acquire significant amounts of these isotopes *in vivo*. The mechanism of acquisition is not clear and it cannot be assumed that the absolute amount of calcium and phosphorus in these tissues has been increased. It is, therefore, probable that an exchange takes place between the normal calcium and phosphorus atoms in the calcified tissues and the radioactive

atoms in the plasma or saliva. Both in vitro and in vivo experiments have demonstrated that dentin acquires radioactive calcium or phosphorus about 6 to 10 times as rapidly as does enamel. This difference between enamel and dentin is probably partially due to the fact that the dentin crystallites are only about one-tenth the size of the enamel crystallites and therefore dentin has a much larger surface area. Another reason for this difference is that dentin is traversed by the so-called dentinal tubules which extend from the pulp cavity to the dentino-enamel junction. These tubules offer a more or less free path for movement of ions within the dentin.

It has been demonstrated by in vivo experiments with radioactive phosphorus that enamel can acquire this isotope both from the saliva and from the plasma via the dentin. Similarly, in vitro experiments have shown that phosphorus can traverse apparently normal enamel and thereby reach the dentin, so that presumably in vivo dentin acquires its radiophosphorus from the saliva as well as from the plasma though much the greater amount reaches it from the plasma.

Actually the amount of calcium and phosphorus which "exchanges" is such a small fraction of the total that it would require a great many years to renew completely all of the calcium and phosphorus atoms in teeth.

**Magnesium:** This element exists only in small amounts in the mineral phase of teeth but it is not of adventitious occurrence. Diets deficient in magnesium will, within a few days, produce serious interferences in tooth formation. The

function of the ameloblasts is disturbed and an atrophy of the odontoblasts occurs. However, the first and most characteristic effect of magnesium deficiency on the teeth is a sudden retardation of dentin calcification.<sup>41</sup> Again, as in the case of some other deficiencies, the band of predentin increases in width. When animals on such a deficient diet are returned to an adequate diet, the degree and rhythm of dentin calcification return to normal in a few days but the abnormal dentin formed during the period of magnesium deficiency is not corrected. Long periods of inadequate magnesium intake cause marked disturbances in the character of the enamel.<sup>42</sup>

**Fluorine.** As we have previously seen fluorine can replace the hydroxyl groups in hydroxyapatite. With one possible exception it is the fluorine which is carried by the drinking water, rather than that occurring in the food, which becomes incorporated in the mineral phases of enamel and dentin. The teeth of about 10 per cent of the individuals who have grown up in communities in which the drinking water contains one part per million of fluorine exhibit mottled enamel<sup>43, 44</sup> which may be regarded as a clinical sign of the primary condition known as endemic dental fluorosis. In communities in which the fluorine concentration exceeds one p.p.m. the percentage of individuals showing mottled enamel and the severity of the mottling increases. Mottled enamel is characterized by patches of chalky white enamel which frequently become pigmented. Chemically the enamel is found to contain an increased amount of fluorine. In severe cases the mottled teeth are structurally

inferior to normal teeth but at the same time they appear to be more resistant to dental caries. Evidence is at hand that the enamel of sound teeth which show no mottling contains significantly more fluorine than the sound enamel of carious teeth.<sup>13, 45</sup> Also epidemiological<sup>46-52</sup> studies have shown a lower incidence of dental caries in regions of endemic mottled enamel.

Fluorine is unique in that it is only in regard to this element that any evidence has been produced that the actual composition of fully developed enamel and dentin may be secondarily altered. Two investigations<sup>53, 54</sup> have established the fact that in experimental animals the fluorine content of the enamel and dentin of mature erupted teeth can be increased by the use of water borne or dietary fluorine. It has also been demonstrated in vitro that the mineral phase of enamel is able to acquire radioactive fluorine from a solution. Thus it is probable that topical applications of fluorine to erupted teeth may increase the fluorine content of enamel. Two preliminary studies<sup>55, 56</sup> on the topical application of fluorine have indicated a decreased incidence of dental caries in the treated patients but as yet no chemical analyses have been carried out on the enamel of the treated teeth.

**Endocrine Factors:** Parathyroidectomy in the rat results in poor calcification of the post-operative incisal dentin with the result that the incisors fracture in from 4 to 6 weeks after removal of the parathyroids.<sup>57</sup> Similarly injections of parathormone, which produce a rise in blood calcium at the expense of bone calcium, produce a simultaneous hypocalcification of dentin

followed by a hypercalcified band of dentin as the blood calcium returns to normal.<sup>58</sup>

Administration of thyroxine induces precocious eruption of rat incisors<sup>59</sup> whereas thyroidectomy results in retarded eruption of the teeth of rats, dogs, pigs and rabbits.<sup>60, 61</sup> Defective tooth structure is common in cretins indicating a probable relationship between thyroid function and tooth development in man.

Adrenalectomy in the rat produces characteristic disturbances in the calcification of dentin. The incisal predentin contains disseminated globules of varying size, suggestive of premature calcification, and the post-operative dentin presents a picture of hypercalcification.<sup>62</sup>

Castration apparently causes no significant chemical or histological changes in rat incisors but the incisors of similarly treated ground squirrels show a definite disturbance of calcification.<sup>63</sup>

Hypophysectomy results, within a week, in a retardation in the eruption of rat incisors.<sup>64, 65</sup> The eruption is progressively delayed so that a complete cessation can be observed in animals that survive the operation one year or longer. Appositional growth is also retarded<sup>66</sup> but to a lesser extent than eruption so that some growth can be observed after eruption has ceased, with the result that the newly formed and uncalcified enamel and dentin at the basal end of the incisors become folded and misshapen. In hypophysectomy the predentin is globular in nature and the post-operative dentin is hypercalcified. Since this same picture is seen in adrenalectomy it is pos-

sible that this effect of hypophysectomy is mediated via the adrenals.

### The Problem of Dental Caries

Dental caries is the most prevalent chronic disease occurring in man and its control would be of great practical importance. The dental literature contains an abundance of conflicting opinion due largely to inadequately controlled experimentation.

The first detailed theory of the mechanism of dental caries was put forward by Miller<sup>67, 68</sup> some 60 years ago. This theory does not attempt to answer the problem of the individual susceptibility to caries but aside from this it remains today as an adequate working basis for further research. The following quotations<sup>68</sup> express the substance of Miller's theory:

Dental decay is a chemico-parasitical process consisting of two distinctly marked stages: decalcification or softening of the tissue, and dissolution of the softened residue. In the case of enamel, however, the second stage is practically wanting, the decalcification of the enamel practically signifying its total destruction.

... the acids which effect decalcification ... are derived chiefly from particles of amylaceous and saccharine substances which lodge in the retaining-centers and there undergo fermentation ...

... all micro-organisms of the human mouth which possess the power of exciting an acid fermentation of foods may and do take part in producing the first stage of caries; ... all possessing a peptonizing or digestive action upon albumin-

ous substances may take part in the second stage; ... whether there is any one bacterium which may always be found in decayed dentine, and which might therefore be entitled to the name of the bacterium of tooth-decay, or whether there are various kinds which occur with considerable constancy, we are not able to say.

At least two varieties of dental caries may be distinguished by their clinical and pathologic differences. The first and distinctly more common variety attacks the teeth of children and young persons predominately, occurs either in the pits or fissures of the crown, or in the neighborhood of points of contact of approximating teeth, penetrates the surface with only sharply localized destruction of enamel, spreads widely in dentin, and approaches the pulp relatively rapidly. The second and less common variety attacks the teeth principally of adults, appears in the gingival area of the crown or in the exposed roots, produces a large aperture at the surface, and penetrates at a varying rate, often very slowly.

Evidence from routine roentgenograms and from Grenz-ray photographs<sup>69</sup> of incipient lesions indicates that radiolucent areas of enamel may be present before surface continuity is lost—a finding interpretable only as a demineralization. Microscopic examination of enamel partially disorganized by caries likewise reveals an altered appearance of enamel rods which can be duplicated closely by in vitro decalcification<sup>70</sup> of enamel fragments in weak acids.

Several micro-organisms which generally inhabit the oral cavity,



notably *Lactobacillus acidophilus* and *Streptococcus salivarius*, have the ability to ferment carbohydrates with the formation of acids. One or more of these organisms may well provide the acid which brings about enamel decalcification. In the case of *L. acidophilus* there is a distinct correlation between the occurrence of the organism in the saliva and the presence of active dental caries.<sup>71</sup> Persons whose teeth have never been attacked by caries rarely, and apparently only accidentally, have these organisms in their saliva. Furthermore, it is impossible to infect these individuals with the organism and they therefore appear to possess some type of immunity. On the other hand, persons with active caries may have 50,000 or more organisms per cubic centimeter of saliva. Another interesting finding is that a high *L. acidophilus* count occurs several months before caries can be clinically diagnosed. However, as yet it is not known how long a period of time elapses between the onset of a carious process and the stage at which it may be clinically diagnosed.

Dietary factors can markedly alter the bacterial count. For instance, a number of cases have been reported in which the elimination of sugar from the diet has reduced the *L. acidophilus* count from 50,000 to 500 within 48 hours and restriction of carbohydrate in the diet has still further reduced the count. In connection with this dietary control of the bacterial count it will be recalled that caries can be experimentally induced in rats by the use of a diet containing coarse cereal particles.<sup>72</sup> The particles apparently become packed in the occlusal fissures and furnish a substrate for

acid formation by bacteria. Although this has not been adequately tested in man it remains a distinct possibility that hard or compact carbohydrate foods may lead to dental caries.

An interesting comparison has been made between endemic dental fluorosis and the salivary count of *L. acidophilus*.<sup>73</sup> It was found that only 15 per cent of the children in a community in which the water supply contained 1.9 p.p.m. of fluorine had bacterial counts over 30,000 per cubic centimeter of saliva whereas 52 per cent of the children in a neighboring community whose water supply had only 0.2 p.p.m. of fluorine were found to have counts over 30,000. The incidence of caries in the latter community was three times as great as in the former.

Although as yet there has been no correlation found between caries activity and the number of streptococci found per cubic centimeter of saliva it has been pointed out<sup>74</sup> that these streptococci are often 1000 times as prevalent as the lactobacilli. Furthermore, it has been shown that cultures of streptococci will dissolve as much tooth tissue in 8 hours as cultures of lactobacilli will dissolve in 24 hours. Consequently, we are not, in the present state of our knowledge, justified in indicating any single microorganism as being the sole one responsible for the decalcification of enamel.

For some time it has been known that lactic acid was formed during the fermentation of glucose by oral bacteria. Recently however, several of the intermediate products of carbohydrate degradation that are known to be formed in the cycles



of glucose utilization by yeast and muscle have also been identified during the fermentation of glucose by salivary organisms.<sup>75, 76</sup> Thus it is possible that such acids as pyruvic and phosphoglyceric, as well as lactic, may be important agents in the decalcification of dental tissues.

Micromethods of analysis have shown caries of dentin to result in simultaneous decalcification and loss of organic matter.<sup>77</sup> In the carious zone closest to normal dentin a proportionally greater loss of organic material than of inorganic substance has been observed. This raises some doubt that beginning caries is solely the result of decalcification. In this connection, another worker<sup>78</sup> has claimed to have observed the production of enamel lesions by the action of proteolytic organisms in cultures in which the reaction never became acid.

The complexity of the problem of dental caries may now be readily appreciated. Many avenues of study have been opened and partially explored. The necessity of further intense research will be realized when it is recalled that dental caries is our most prevalent chronic disease.

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# BIBLIOGRAPHY

- <sup>1</sup> Schour, I. and Hoffman, M. M.: *J. Dent. Res.*, 15: 161 (1935).
- <sup>2</sup> Schour, I. and Poncher, H. G.: *Am. J. Dis. Child.*, 54: 757 (1937).
- <sup>3</sup> Chase, S. W.: *J. Am. Dent. Assn.*, 22: 1343 (1935).
- <sup>4</sup> Brekhus, P. J. and Armstrong, W. D.: *J. Dent. Res.*, 15: 23 (1935).

- <sup>5</sup> Manly, R. S. and Hodge, H. C.: *J. Dent. Res.*, 18: 133 (1939).
- <sup>6</sup> Crowell, C. D., Hodge, H. C. and Line, W. R.: *J. Dent. Res.*, 14: 251 (1934).
- <sup>7</sup> Kramer, B. and Tisdall, F. F.: *J. Biol. Chem.*, 48: 223 (1921).
- <sup>8</sup> Fiske, C. H. and Subbarow, Y.: *J. Biol. Chem.*, 66: 375 (1925).
- <sup>9</sup> Armstrong, W. D.: *Ind. and Eng. Chem.*, 8: 384 (1936).
- <sup>10</sup> Armstrong, W. D. and Brekhus, P. J.: *J. Biol. Chem.*, 120: 677 (1937).
- <sup>11</sup> Harrison, H. E.: *J. Biol. Chem.*, 120: 547 (1937).
- <sup>12</sup> Steadman, L. T., Hodge, H. C. and Horn, H. W.: *J. Biol. Chem.*, 140: 71 (1941).
- <sup>13</sup> Armstrong, W. D. and Brekhus, P. J.: *J. Dent. Res.*, 17: 393 (1938).
- <sup>14</sup> Engel, L. L.: *J. Dent. Res.*, 14: 273 (1934).
- <sup>15</sup> Drea, W. F.: *J. Dent. Res.*, 15: 403 (1936).
- <sup>16</sup> Lowater, F. and Murray, M. M.: *Biochem. J.*, 31: 837 (1937).
- <sup>17</sup> Le Fevre, M. L., Bale, W. F. and Hodge, H. C.: *J. Dent. Res.*, 16: 85 (1937).
- <sup>18</sup> Gruner, J. W., McConnell, D. and Armstrong, W. D.: *J. Biol. Chem.*, 121: 771 (1937).
- <sup>19</sup> Mathis, H.: *Deut. Zahn-, Mund-, Kieferheilk.*, 5: 114 (1938).
- <sup>20</sup> Thewlis, J., Glock, G. E. and Murray, M. M.: *Trans. Faraday Soc.*, 35, 358 (1939).
- <sup>21</sup> Bale, W. F., LeFevre, M. L. and Hodge, H. C.: *Naturwissenschaften*, 40: 636 (1936).
- <sup>22</sup> Bale, W. F., Hodge, H. C. and Warren, S. L.: *Am. J. Roentgenol. Radium Therapy*, 32: 369 (1934).
- <sup>23</sup> Bale, W. F.: *Am. J. Roentgenol. Radium Therapy*, 43: 735 (1940).
- <sup>24</sup> Gruner, J. W. and McConnell, D.: *Z. Krist.*, 97: 208 (1937).
- <sup>25</sup> French, E. L., Welch, E. A., Simmons, E. J., Le Fevre, M. L. and Hodge, H. C.: *J. Dent. Res.*, 17: 401 (1938).
- <sup>26</sup> Warren, S. L., Bishop, F. W., Hodge, H. C. and Van Huysen, G.: *Am. J. Roentgenol. Radium Therapy*, 31: 663 (1934). (See also four papers in vol. 34, and two papers in each of vols. 36, 37, 40 of the same journal under the title "Factors influencing the quantitative measurement

of the roentgen-ray absorption of tooth slabs.")

<sup>27</sup> "Procedures in Experimental Physics" by John Strong. Published by Prentice-Hall, Inc., 1939. See Chapter VII.

<sup>28</sup> Gomori, G., *Proc. Soc. Exp. Biol. Med.*, 44: 250 (1940).

<sup>29</sup> Wolbach, S. B. and Howe, P. R.: *Am. J. Path.*, 9: 275 (1933).

<sup>30</sup> Schour, I., Hoffman, M. M. and Smith, M. C.: *Am. J. Path.*, 17: 529 (1941).

<sup>31</sup> Boyle, P. E.: *Am. J. Path.*, 14: 843 (1938).

<sup>32</sup> Karshan, M. and Rosebury, T.: *J. Dent. Res.*, 13: 305 (1933).

<sup>33</sup> Rosebury, T. and Foley, G.: *J. Dent. Res.*, 14: 359 (1934).

<sup>34</sup> Rosebury, T., Karshan, M. and Foley, G.: *J. Am. Dent. Assn.*, 22: 98 (1935).

<sup>35</sup> Campbell, W. W. and Greenberg, D. M.: *Proc. Nat. Acad. Sci.*, 26: 176 (1940).

<sup>36</sup> Unpublished data from authors' laboratory.

<sup>37</sup> Hevesy, G. and Armstrong, W. D.: *J. Biol. Chem.*, 133: xliiv (1940).

<sup>38</sup> Volker, J. F. and Sognnaes, R. F.: *J. Dent. Res.*, 19: 292 (1940).

<sup>39</sup> Sognnaes, R. F. and Volker, J. F.: *Am. J. Physiol.*, 133: 112 (1941).

<sup>40</sup> Barnum, C. P. and Armstrong, W. D.: *Am. J. Physiol.*, 135: 478 (1942).

<sup>41</sup> Irving, J. T.: *J. Physiol.*, 99: 8 (1940).

<sup>42</sup> Becks, H. and Furuta, W. J.: *J. Am. Dent. Assn.*, 28: 1083 (1941).

<sup>43</sup> Dean, H. T.: *J. Am. Med. Assn.*, 107: 1269 (1936).

<sup>44</sup> Dean, H. T. and Elvove, E.: *Am. J. Pub. Health*, 26: 567 (1936).

<sup>45</sup> Armstrong, W. D.: *J. Biol. Chem.*, 119: v (1937).

<sup>46</sup> Dean, H. T., Arnold, F. A. and Elvove, E.: *U. S. Pub. Health Repts.*, 57: 1155 (1942).

<sup>47</sup> Arnim, S. S., Aberle, S. D. and Pitney, E. H.: *J. Am. Dent. Assn.*, 24: 478 (1937).

<sup>48</sup> Dean, H. T.: *U. S. Pub. Health Repts.*, 53: 1443 (1938).

<sup>49</sup> Day, C. D. M.: *Brit. Dent. J.*, 68: 409 (1940).

<sup>50</sup> Ockerse, T. and Meyer, H. D.: *S. African Dent. J.*, 15: 62 (1941).

<sup>51</sup> Wilson, D. C.: *Lancet*, 1: 375 (1941).

<sup>52</sup> Klein, H. and Palmer, C. E.: *U. S. Pub. Health Bull.*, No. 239 (1938).

<sup>53</sup> Perry, M. W. and Armstrong, W. D.: *J. Nutrition*, 21: 35 (1941).

<sup>54</sup> McClure, F. J.: *Sci.*, 95: 256 (1942).

<sup>55</sup> Bibby, B. G.: *J. Dent. Res.* In press.

<sup>56</sup> Cheyne, V. D.: *J. Am. Dent. Assn.*, 29: 804 (1942).

<sup>57</sup> Erdheim, J.: *Mitt. a. d. Grenzgeb.*, 16: 632 (1906).

<sup>58</sup> Schour, I. and Ham, A. W.: *Arch. Path.*, 17: 22 (1934).

<sup>59</sup> Karnofsky, D. and Cronkite, E. P.: *Proc. Soc. Exptl. Biol. Med.*, 40: 568 (1939).

<sup>60</sup> Biedl, A.: *Korrespbl. Zahnarzte*, 55: 99 (1931).

<sup>61</sup> Kranz, P.: *Dent. Zahnheilk. in Vortragen*, 32: 3 (1914).

<sup>62</sup> Schour, I. and Rogoff, J. M.: *Am. J. Physiol.*, 115: 334 (1936).

<sup>63</sup> Schour, I.: *Anat. Rec.*, 65: 177 (1936).

<sup>64</sup> Schour, I. and van Dyke, H. B.: *Am. J. Anat.*, 50: 397 (1932).

<sup>65</sup> Schour, I. and van Dyke, H. B.: *Proc. Soc. Exptl. Biol. Med.*, 29: 378 (1932).

<sup>66</sup> Schour, I.: *Angle Orthod.*, 4: 3 (1934).

<sup>67</sup> Miller, W. D.: *Arch. f. exp. Path. u. Pharm.*, 16: 291 (1882).

<sup>68</sup> Miller, W. D.: "The Micro-organisms of the Human Mouth," Philadelphia, S. S. White Company (1890).

<sup>69</sup> Applebaum, E.: *Dent. Cosmos*, 77: 931 (1935).

<sup>70</sup> Williams, J. L.: *Dent. Cosmos*, 39: 269, 355 (1897).

<sup>71</sup> Jay, P.: "Dental Science and Dental Art," Lea and Febiger (1938), Chapter X. Edited by Samuel Gordon.

<sup>72</sup> Rosebury, T., Karshan, M. and Foley, G.: *J. Am. Dent. Assn.*, 21: 1599 (1934).

<sup>73</sup> Jay, P.: *Publication Am. Assn. Adv. Sci.*, 19: 63 (1942).

<sup>74</sup> Bibby, B. G.: "Dental Caries," Univ. Penna. Bicent. Conf., Univ. of Penna. Press (1941), p. 27.

<sup>75</sup> Fosdick, L. S., Campaigne, E. E. and Fancher, O.: *Illinois Dent. J.*, 10: 85 (1941).

<sup>76</sup> Fosdick, L. S. and Starke, A. C.: *J. Am. Dent. Assn.*, 28: 234 (1941).

<sup>77</sup> Manly, R. S. and Deakins, M. L.: J. Dent. Res., 19: 165 (1940).

<sup>78</sup> Pincus, P.: Brit. Dent. J., 63: 511 (1937).

## TELEOSTS

The most populous order of the class pisces of the subphylum vertebrata. The true bony fishes.

## TELEPHIIN

A glucoside from the leaves and root of *Sedum telephium*.

## TEMPERATURE

### REGULATION, PHYSICAL

Maintenance of constant body temperature by changing the thermal insulation and rate of evaporation without changing the metabolic rate when environmental temperature changes. Mainly at high environmental temperatures.

M. K.

## TEMPERATURE

### REGULATION, CHEMICAL

Maintenance of constant body temperature by changes in the metabolic rate when environmental temperature changes. Mainly at low environmental temperatures.

M. K.

## TEMULINE

An alkaloid, a base of the pyridine series from the seed of *Lolium temulentum*; a nerve poison.

## TEPHROSIN

Hydroxydeguelin;  $C_{23}H_{22}O_7$ , occurs in derris, cubé root, m.p. 198°; toxic to fish, crustacea, insects, but not to humans.

## TERATOLOGY

The study of malformations and monstrosities in organisms.

## TEREBENE

A mixture of terpene hydrocarbons, chiefly dipentene and terpinene, prepared from oil of turpentine; b.p., 160-172°; sp. gr., 0.860-0.865; used as expectorant,

antiseptic, antifermentative; internally in bronchitis, genito-urinary inflammations and other ailments.

## TERMONES

Male determining factors, e.g. safranal, a carotenoid aldehyde, for certain algae.

## TERPINENES

Monocyclic terpenes; alpha-form found in coriander, cardamom, marjoram; beta-form synthetic; gamma-form in coriander, lemon, Ajowan oils.

## TERPINENOLS

Monocyclic alcohols found in terpineol, cardamom, cypress, marjoram and nutmeg oils.

## TERPINEOL

Lilacin; in commercial form, a mixture of several isomers used in perfumes and denaturant of fats in soap mfg.

## TERPINEOLS

$C_{10}H_{17}OH$ , monocyclic alcohols, dehydration products of terpin; alpha-form, d-rotatory found in petit-grain, neroli, etc., l-rotatory in camphor oils, both in cajuput oil; beta-form not found in nature; gamma-form may exist in nature.

## TERPIN HYDRATE

Di-penteneglycol;  $C_{10}H_{20}O_2 \cdot H_2O$ ; m.p. 115-117° used as expectorant, antiseptic.

## TERPINOLENE

Monocyclic terpene of terebine, of doubtful purity.

## TESTOSTERONE

$C_{19}H_{28}O_2$ , m.p. 154°, the male sex hormone found in the interstitial cells of the testes and prepared synthetically from cholesterol; is probably metabolized to andro-

sterone; acetate, m.p. 140-141° and a benzoate, m.p. 194-196°.

# **TETANUS**

A disease caused by *Bacillus tetani* (*Clostridium tetani*) which may enter by a most trivial wound and whose toxins affect the central nervous system to produce spasm. Antitoxin or toxoid therapy is employed.

# **TETANUS ANTITOXIN**

Purified antitetanic serum; concentrated or refined Tetanus antitoxin; antitetanic globulins; a sterile aq. soln. of antitoxic substances from blood serum or plasma from immunized horse.

# **TETRAHYDROPYRROLE**

See Pyrrolidine.

# **TETRAMETHYLAMMONIUM HYDROXIDE**

May be the "sting" of jellyfishes, acts like curare.

# **TETRANDRINE**

$C_{38}H_{42}O_6N_2$ ; m.p. 217-218°; an alkaloid present in the Chinese drug Han-Fang-Chi; affects respiratory and skeletal muscle.

# **TETRASACCHARIDASES**

See Enzymes, Non-proteolytic.

# **TETROSE**

Any carbohydrate with four carbon atoms; there are four aldotetroses and two keto-tetroses.

# **THALAMUS**

See Nervous System.

# **THALLINE**

An alkaloid, 6-methoxy-1,2,3,4-tetrahydroquinoline,  $C_{10}H_{13}ON$ ; white light-sensitive cryst.; m.p. 42-43°; b.p. 283-285°; its salts have antiseptic and antipyretic action.

# **THALLOPHYTA**

See Microbiology.

# **THAPSIAC ACID**

$C_{18}H_{30}O_4$ ; a saturated dibasic fatty acid found in Conifer Wax.

# **THEBAINE**

$C_{19}H_{21}O_3N$ ; leaflets or prisms, m.p. 193°; dimethylmorphine; paramorphine; an alkaloid occurring in opium to an extent of less than 1%; produces a blood-red color with  $H_2SO_4$ ; is a convulsant and not narcotic. Use in medicine is as a starting point for non-addicting morphine substitutes and as a diuretic.

# **THEELIN**

See Estrin or Estrone.

# **THEEOL**

See Estriol.

# **THEINE**

See Caffeine.

# **THELEPHORIC ACID**

A violet crystal pigment of the fungus telephora. It is a dicarboxy, polyoxy phenanthrene derivative.

# **THEOBROMINE**

Xantheose;  $C_7H_8O_2N_4$ ; 3:7-dimethylxanthine, sublimes 290°; alkaloid of cacao, milder than caffeine, used as diuretic and myocardial stimulant.

# **THEOBROMINE TESTS**

See Stroup, Winkler.

# **THEOCIN(E)**

See Theophylline.

# **THEOPHYLLINE**

Theocin(e); 1:3-dimethylxanthine, m.p. 269-272°; found in tea; resembles caffeine and theobromine, diuretic.

# **THEOPHYLLINE TESTS**

See Plummer-Mendenhall, Winkler.

# **THERAPEUTICS**

See Pharmacology.

# **THERAPIC ACID**

An 18 carbon fatty acid with four double bonds.

# **THERAPY, FEVER**

See Fever Therapy.

# **THERMOGENETIC HORMONES**

Hormones which promote liberation of heat so as to raise basal metabolic rate, e.g. epinephrine and sympathin.

# **THERMOGENIC EFFECT**

Increase of animal's body temperature resulting from food drugs or other substances or from other influences such as diathermy or high environmental temperature.

M. K.

# **THERMOLABILE**

Decomposed by heat.

# **THERMOTROPISM**

Reaction of a living form to heat.

# **THEVETIN**

$C_{24}H_{46}O_{18}$ ; a glucoside from the seed of *Thevetia nereifolia* of the digitalis group, b.p.  $210^{\circ}$ .  
See Digitalis.

# **THIAMIN**

See also Choline, Vitamin B<sub>1</sub>.

# **THIAMIN CHLORIDE**

$C_{12}H_{17}N_4OSC_1$ ; vitamin B<sub>1</sub>; the anti-neuritic vitamin. The vitamin associated with carbohydrate metabolism. Found in yeast, meat, fish, milk, eggs, etc. Insufficiency causes syndrome and dermatitis. The hydrochloride, m.p.  $232-4^{\circ}C$ . is water soluble and is used therapeutically.

See also Carbohydrate Metabolism.

# **THIAMINOPROTEIN ENZYMES**

Enzymes concerned with the

breakdown of pyruvic acid which contain diphosphothiamine as the prosthetic group; include carboxylase (yeast), pyruvic oxidase (bacteria), pyruvic oxidase (animal tissue).

# **THIAMIN**

# **PYROPHOSPHATASE**

See Enzymes, Non-proteolytic.

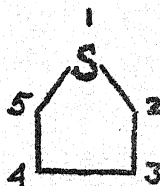
# **THIAMIN, ROLE IN PLANTS**

See Plant Growth Hormones.

# **THIASINE**

See Ergothioneine.

# **THIAZOLE RING**



# **THIGMOTROPISM**

Reaction of a living form to contact.

# **THIOBACTERIALES**

See Microbiology.

# **THIOCHROME**

Coloring matter of yeast,  $C_{12}H_{14}ON_4S$ , an oxidation product of vitamin B<sub>1</sub>, fluoresces blue in alkaline or neutral solution, m.p.  $228^{\circ}$ ; physiologically almost inactive.

# **THIOCYANOGEN NUMBER**

The number of milligrams of thiocyanogen ( $SCN$ )<sub>2</sub>, which will add on to 1 gram of a fat or a mixture of fatty acids. Only one double bond of linoleic acid reacts with thiocyanogen. This together with the iodine number enables one to calculate the amount of linoleic acid present.

# **THIONEINE**

Ergothioneine. The betaine of

thiolhistidine. Found in the red cells in human blood, where its concentration is 10-25 mg.%, in yeast and in ergot.

See Ergothioneine.

## THIORHODACEAE

See Photosynthesis.

## THIO-SUGARS

Sugars in which a sulfur atom replaces an oxygen atom, e.g. methyl thiopentose of yeast.

## THIXOTROPY

A term introduced in 1927 to describe those colloidal systems in which a gel is isothermally converted into a sol by shaking or stirring the gel, the sol setting to a gel again when left undisturbed. Two examples are starch in water, and quicksand.

## THORN APPLE

See Stramonium.

## THORAX

See Respiration.

## THREONINE

$\alpha$ -amino- $\beta$ -hydroxy-n-butyric acid. Needles or hexagonal plates. An indispensable amino acid found in fibrin, and many other proteins in small amounts.

## d(-)THREONINE

### METABOLISM

$\beta$ -oxidation occurs, yielding  $\alpha$ -amino- $\beta$ -ketobutyric acid, which further oxidizes to acetic acid and glycine.

## THREOSE

One of the tetrose sugars, has l- and d- forms (aldehyde).

## THROMBASE

See Thombin.

## THROMBIN

Thrombase; the protease enzyme which converts fibrinogen to fibrin in the clotting process; is formed from a precursor, pro-

thrombogen) by the action of an activator, thrombokinas, and Ca ions.

## THROMBOKINASE

An activator in the formation of thrombin in the clotting process from prothrombin normally present in the blood.

## THROMBOPLASTIN

An early name for cephalin, or a cephalin-protein combination.

## THROMBOPLASTIN

### SOLUTION

Soln. of brain extract in NaCl; used as hemostatic.

## THROMBOSIS

Clotting within a blood vessel. The clot is called a thrombus.

## THUJA

Dried leafy young twigs of *Thuja occidentalis* containing thujone and other components and used as antipyretic, expectorant, antihelminthic, irritant.

## THUJENE

A dicyclic terpene present in alpha and beta-form in various oleoresins (*Boswellia serrata*).

## THUJONE

$C_{10}H_{16}O$ , a constituent of many essential oils; b.p. 199-202°.

## THUJYL ALCOHOL

Secondary dicyclic terpene alcohol of wormwood oil.

## THUNBERG TUBES

Vessels for the study of oxidation of tissues, in which one can prevent reoxidation, e.g. of methylene blue, by evacuating the air.

## THYME

Dried leaves and flowering tops of *thymus vulgaris* containing volatile oil, tannin, and gum; used as diaphoretic, stimulant, carminative.



**THYMIDINE**

3 - thymine - d - desoxyriboside, a nucleoside of desoxyribonucleic acids.

**THYMINE**

5-methyl-2:6-dioxytetrahydropyrimidine,  $C_5H_8O_2N_2$ , m.p. 321-325°; a constituent of nucleic acids of animal origin.

**THYMINE TESTS**

See Hunter, Johnson-Clapp.

**THYMINOSE**

d-2-desoxyribose; a constituent of thymonucleic acid.

**THYMOCRESCIN**

See Thymus Principle.

**THYMOL**

3-hydroxy-p-cymene; constituent of oil of thyme, etc., m.p. 51.5°; used as disinfectant.

**THYMOL BLUE**

Thymolsulfonephthalein,  $C_{27}H_{30}O_5S$ ; a brownish-green, cryst. powder; used as acid-base indicator: red at pH 1.2 to yellow at 2.8; also yellow at 8.0 to blue at 9.6.

**THYMOL IODIDE**

$(C_6H_2 \cdot CH_3 \cdot OI \cdot C_3H_7)_2$ ; used as antiseptic in place of iodoform.

**THYMOLPHTHALEIN**

A pH indicator; colorless 9.3 to blue 10.5; also used as reagent for blood.

**THYMONUCLEIC ACID**

See Genetics.

**THYMUS**

A ductless glandlike body situated in the anterior mediastinal cavity which reaches its maximum development during the early years of childhood; greyish-red; usually has two longitudinal lobes joined across a median plane.

**THYMUS PRINCIPLE**

A hormone of the thymus gland which speeds up cell proliferation and growth up to puberty. Its injection in successive generations has been claimed to produce precociousness. A purified extract, called thymocrescin, is claimed to be a sulfur-containing polypeptide.

**THYNNIN**

A protamine of the tuna fish.

**THYR(E)OGLOBULIN**

A conjugated protein of the thyroid gland, which to a very large extent is responsible for the activity of the gland. It consists of a protein in conjugation with the iodine containing amino acid thyroxin.

**THYROID**

Thyroid gland of domesticated animals that are used as food by man, freed from connective tissue and fat, dried and powdered; a yellowish powder, saline taste; used in thyroid deficiency; alterative; in myxedema, obesity, mental affections, etc.

**THYROID AND EMOTION**

See Psychiatry, Biochemistry of.

**THYROTOXICOSIS**

See Goiter.

**THYROTROPIC PRINCIPLE**

A protein-like hormone of the anterior lobe of the pituitary, having direct control of the formation of the thyroid hormone.

**THYROXIN(E)**

$C_{15}H_{11}O_4NI_4$ ; m.p. about 231-233°; the active component of the hormone of the thyroid glands, appearing in l-form; promotes general metabolism and growth; dose 0.2-2 mgm.

See also Teeth, Biochemistry of.

**TIGLIC ACID**

$C_5H_8O_2$ ; an unsaturated fatty acid found in croton oil. Has one double bond, m.p.  $64.5^\circ C$ .

**TIGOGENIN**

$C_{27}H_{44}O_3$ ; 3-hydroxy-sapogenin; the non-sugar residue of the digitalis saponin, tigonin.

**TILIACORINE**

An alkaloid,  $C_{30}H_{27}NO_2(CH_3O)_2$ ; m.p.  $260-261^\circ$ ; from the bark of *tiliacora acuminata* Miers, Menispermaceae; a cardiac and respiratory poison.

**TILIADIN**

An amaroid,  $C_{21}H_{32}O_2$ , from fresh bark of *Tilia ulmifolia*; m.p.  $228-229^\circ$ ; b.p.  $360^\circ$ .

**TIMBOIN**

An amaroid from root of *Serjania curassavica*; is a fish poison.

**TINCTURE IODINE**

Contains 6.5-7.5 gm. iodine, 4.5-5.5 gm. potass. iodide per 100 cc. soln.; alcohol 80-85% by volume; used as antiseptic, disinfectant for skin surfaces, abrasions, ulcers, etc.; in glandular and lymphatic enlargements; also in arthritis, and other ailments.

**TINCTURE IODINE, MILD**

1.8-2.2 gm. Iodine and 2.1-2.5 gm. sod. iodide per 100 cc. of soln.; used as skin disinfectant.

**TISSUE DESTRUCTION**

See Wound Healing.

**TISSUES, PERIODONTAL**

See Teeth, Biochemistry of.

**TITRE**

In general the amount of one substance required to react with a given volume of another substance, as the amount of acid required to neutralize a definite amount of base. In the analysis of fats and oils, the titre refers to

the temperature at which the fatty acids obtained by alkaline hydrolysis of the fat, resolidify.

**T.N.**

Turnover number, referring in enzyme study to the number of molecules of an enzyme or coenzyme reacting per minute at a given temperature.

**$\alpha$ -TOCOPHEROL**

Vitamin E; the vitamin necessary to avoid reproductive failure and a type of male sterility. It also has a growth stimulating effect. It has been found in wheat germ oil, other seed oils and in various organs via the food. The leaves of alfalfa and lettuce are a good source.

Reference: Evans, Emerson, Jour. Biol. Chem., 113, 319 (1936).

**TOLERATED DOSE**

See Chemotherapy.

**TÖPFER'S REAGENT**

Dimethyl-amino-azo-benzene, an indicator that changes from red through pink to yellow, as pH changes from 3 to 4.

**TOPICAL AGENTS**

See Wound Healing.

**TORINGIN**

A glucoside,  $C_{21}H_{20}O_9 \cdot 2H_2O$ , from bark of *Pirus toringa*; m.p.  $135-137^\circ$ .

**TORTELLI-GAFFE TEST FOR LIVER OILS AND ERGOSTEROL**

One cc. of oil is mixed with 6 cc. chloroform and 1 cc. ice-cold glacial acetic acid, followed by the addition of 4 drops of a 10% chloroform solution of bromine. Liver oil from sea animals changes from reddish to green within a minute; hydrogenated fish oils give a similar but stronger reaction; oil from land

animals does not react. Ergosterol gives the same test.

Reference: Chem. Ztg. 1915, 14.

## TORULA

See Microbiology.

## TORULIN

A name originally applied to crude vitamin B<sub>1</sub> preparations; now occasionally used for the pure thiamin chloride.

## TOSYL GROUP

The para-toluene sulfonyl group, used in making compounds for the study of the structure of sugars, etc.

## TOTAL BASE

The analytical value for the sum of the positive elements, Na, K, Ca, Mg; total mineral cationogens; sometimes called fixed base.

## TOTAL MINERAL ANIONOGENS

The analytical value for the sum of the elements P, S and Cl; sometimes called fixed acid.

## TOTAQUINA

A mixture of the alkaloids from Chinchona bark; used similarly to quinine.

## TOXICAROL

Hydroxydeguelin; C<sub>28</sub>H<sub>22</sub>O<sub>7</sub>; m.p. 218-220°; from derris root, has action like rotenone.

## TOXICOLOGY

Toxicology is the science of poisons. A poison can be defined (according to Peterson, Haines and Webster) as a substance which, when introduced into the body in relatively small quantities and acting chemically, is capable of producing death or serious injury to health in the case of an ordinary individual in average health.

Poisoning may be acute or chronic. In the acute type, the

effect is brought about usually by a large single dose and the toxic symptoms appear promptly and are drastic. In chronic poisoning the symptoms are vague and extend over a period of time. Usually this is due to a slow accumulation of poison brought about by the continuous intake of a lethal substance in an amount slightly in excess of the body's capacity to eliminate it. The latter type is often encountered in industry. Lead, mercury and benzene poisoning can be cited as examples. Cumulative poisoning can also occur in therapy as for instance in digitalis administration.

Sociologically, poisoning may be classed as criminal and accidental. Poison as an instrument of murder has steadily decreased in importance, but as a means of suicide is commonly employed. In war, poisons have been generally limited to lethal gases. Accidental poisonings are numerous in types, but economically, industrial poisons are of paramount importance. With the continuous introduction of new materials in industry the types of poisoning are constantly increasing as illustrated by a recent discovery that metallic magnesium as a contaminant of wounds gives rise to a type of tissue emphysema resembling welchii gas gangrene.

Various classifications of poisons have been proposed. The following is simple and satisfactory:

- I. Inorganic
- II. Organic
  - A. Plant products
  - B. Animal products
  - C. Bacterial toxins
  - D. Synthetic compounds

The range of inorganic poisons is large. It includes acids and alkalis;

salts, particularly of lead, mercury, arsenic, and other heavy metals as well as cyanides and fluorides; many elements such as chlorine and bromine; and sundry compounds.

Among the poisonous plant products the alkaloids occupy an important position. Strychnine, morphine, atropine, and the ergot group are common examples. There are also various poisonous glucosides of which amygdalin is the outstanding example.

As illustrations of poisonous products of animal origin, the snake venoms are of particular interest. The bites of many insects likewise are poisonous. Hormones given in excessive amounts must be considered as toxins. The subject is becoming of increasing importance as potent synthetic hormones are becoming available. The bacterial toxins are usually considered as a separate class and are not extensively treated in toxicology. Ethyl alcohol, the product of yeast fermentations is a potential poison.

The list of synthetic organic compounds is exceedingly large. It is therefore only possible to enumerate a few of the compounds which are frequently encountered as poisons. Phenol is one of the oldest, and is still frequently used for suicide. The hypnotics, particularly chloral and the barbiturates, are often the cause of accidental or intentional death. Many of the simple aromatic compounds including benzene itself and aniline, are important industrial poisons.

The most important paths by which poisons enter the body are by ingestion, by inhalation, by absorption from the skin, and by injection. The intravenous route

usually brings about the most rapid action. Most drugs are more effective when injected than when taken orally. In fact, various substances such as snake venom, certain bacterial toxins, and magnesium salts are only toxic when given parenterally.

The diagnosis of poisoning is based mainly on the history and the symptoms, but the conclusive proof requires isolating and identifying the lethal substance in the stomach and intestinal contents, in the excreta, or in the tissues of the body. Sudden illness in an apparently healthy subject, particularly if the acute onset occurs soon after eating, warrants investigating the possibility of poisoning.

The symptoms of poisoning vary greatly. Usually they are non-specific. Vomiting, diarrhea, intestinal cramps, dyspnoea, acapnea, tachycardia, bradycardia, delirium and convulsions are some of the common findings. A few drugs produce rather specific effects such as the pin point constriction of the pupil in morphine poisoning and the excessive salivation after pilocarpine.

The treatment of poisoning consists first of all in the removal of the toxic agent. If the poison was taken orally gastric lavage or the administration of an emetic is indicated. Gaseous poisons such as carbon monoxide are removed by stimulating respiration with carbon dioxide and giving oxygen. Destruction of the poison remaining in the body is sometimes effective. Oxidation of morphine with potassium permanganate and detoxifying arsenic with sodium thiosulfate may be cited as examples.

Specific antidotes can be given

for certain types of noxious agents. Thus alkalis such as sodium bicarbonate for neutralizing acids, tannates for alkaloids, the nitrites and sodium thiosulfate in treating cyanide poisoning serve as illustrations.

Most important in treatment is combating the symptoms. For the drugs depressing the central nervous system, the stimulants are used. Picrotoxin has been shown to be effective in barbiturate poisoning. Caffeine remains the most available stimulant. For the convulsion drugs the central nervous depressants are indicated. Often poisons produce shock which requires supportive treatment.

The isolation and identification of poisons is a highly specialized science. Standardized methods have been developed for determining the common lethal agents.

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# TOXICODENDROL

See Poison Ivy.

# TOXICODENDRIC ACID

See Poison Ivy.

# TOXINS

See Detoxication, Microbiology.  
See Immunological Phenomena.

# TOXISTEROL

A toxic sterol obtained by continued irradiation of calciferol. See Calciferol.

# TOXOFLAVIN

$C_8H_8N_2O_2$ ; a yellow pigment of cocovenenans which is a violent heart poison, probably isomeric with methylxanthine.

# TOXOIDS

Anatoxins; toxins which have been treated with formaldehyde

or altered in other ways, with the destruction of only the toxic properties but not of antigenic capacity, e.g. diphtheria toxoid. See also Immunological Phenomena.

# TPN

Triphosphopyridinenucleotide, a hydrogen carrier like cozymase.

# TRACHOMA

See Chemotherapy, Conjunctivitis.

# TRAGACANTH

Gum Tragacanth, Goat's Thorn; dried gummy exudation from Asiatic species of Astragalus, Leguminosae; consists of bassorin, pectin, starch; used as demulcent, as base for skin medication; industrially as emulsifier, adhesive, excipient for pills.

# TRAGUS

See Hair.

# TRANSAMINATION

See Amino Acids, Physiology of.

# TRANSMETHYLATION

See Amino Acids, Physiology of, Creatine and Creatinine Metabolism.

# TRANSPHOSPHORYLATION

See Creatine and Creatinine Metabolism.

# TRANSUDATE

The name applied to the filtrate of blood through capillaries, when the normal filtration is modified in a non-inflammatory manner, in the direction of increased accumulation of fluid in the tissues.

# TRASENTIN

Diphenylacetyl - diethylaminoethanol hydrochloride, melting at  $112-114^\circ$ ; used as antispasmodic.

# TRAUMA

Injury.

# TRAUMATIC ACID

The "wound hormone" of plants,



a dibasic acid,  $\text{HOOCCH}=\text{CH}(\text{CH}_2)_8\text{COOH}$ , which induces cell multiplication and healing. See Phytohormones, Plant Growth Hormones.

**TRAUMATIC INFLAMMATION**  
See Wound Healing.

**TRAVAILLE TEST FOR BILE PIGMENTS**

Reagent—2 gm. p-dimethylaminobenzaldehyde, 50 gm. hydrochloric acid and 50 cc. water. The addition of 4 cc. of reagent to 10 cc. of urine gives rise to the formation of a blue color. Reference: Giorn. farm. chim. 62, 310 (1913). Indian Med. Record 43, 138 (1924). J.A.M.A. 83, 564 (1924).

**TREHALASE**

See Enzymes, Non-proteolytic.

**TREHALOSE**

See Disaccharides.

**TRENCH MOUTH**

See Vincent's Angina.

**TREPHONES**

Proteoses which stimulate the growth of cells in tissue cultures. See Wound Healing.

**TRICHINOSIS**

Disease caused by the nematode worm trichina (in man and pig).

**TRICHLORACETIC ACID**

$\text{CCl}_3\text{COOH}$ ; colorless deliquescent crystals which are very caustic and whose aq. soln. is very acid; m.p. 57-58°; b.p. 196-197°; sp.gr., 1.629<sup>61</sup>/<sub>4</sub>; produced by oxidation of chloral with nitric acid; used as escharotic, astringent, hemostatic; also as decalcifier and fixative in microscopy and as protein precipitant.

**TRIFOLIOL**

Sitosterol-d-glucoside belonging to

the phytosterol glucoside group from the flowers of red clover; m.p. 295° with decomposition.

**TRIFOLIIN**

A chromo-glucoside from flowers of red clover, melting at 260°; on hydrolysis yields the coloring matter trifolitin.

**TRIGENOLLIN**

See Trigonelline.

**TRIGGER ACTION**

See Nervous System.

**TRIGONELLIN**

$\text{C}_7\text{H}_9\text{O}_2\text{N}$ ; coffearin; gynesin; trigenollin; Betaine of nicotinic acid. Inert alkaloid of peas, potatoes and many other plants. Hygroscopic prisms, m.p. with one molecule of water 130°C., anhyd. 218°C.

**TRIOBIN**

$\text{C}_{36}\text{H}_{36}\text{O}_5\text{N}_2$ ; m.p. 235°; an alkaloid from the root *Cocculus trilobus*; paralyzes respiration and the heart, lowers blood pressure.

**TRIMETHYLAMINE**

$(\text{CH}_3)_3\text{N}$ ; a colorless gas with a fishy odor; b.p. 3-4°, sp.gr., 0.6709<sup>9</sup>/<sub>4</sub>; occurs in beet sugar residues and herring brine; used in synthesis of organic amino compounds.

**TRIMETHYLAMINE OXIDE**

$\text{C}_3\text{H}_9\text{ON}$ ; m.p. 96°; a nitrogenous base found in marine types, in the muscles of Crustacea and in the urine of cephalopods, also in fish and animal tissues.

**TRIMETHYLXANTHINE**

See Caffeine.

**TRIOSE ENZYME**

The pyridinoprotein enzyme which catalyzes the oxidation of glyceraldehyde, 1(+), or glycollic aldehyde by coenzyme I; optimum pH about 8, very sensitive to iodoacetic acid.



# TRIOSEPHOSPHORIC ENZYME

A pyridinoprotein enzyme which catalyzes the initial oxidation of 3-phosphoglyceraldehyde, m.w. about 100,000, found in brain, skeletal and cardiac muscle, yeast and bacteria.

# TRIOSES

Carbohydrates with 3 carbon atoms; dihydroxyacetone and two stereoisomers of glyceric aldehyde.

# TRIPHAL

Sodium auro-thiobenzimidazol-carboxylate; used as antitubercular.

# TRIPHENYL ETHYLENE

See Estrogens, Synthetic.

# TRIPHOSPHOPYRIDINIUM ENZYMES

Pyridinoprotein enzymes containing coenzyme II, which catalyze the oxidation of substrates such as the hexosemonophosphoric, isocitric and glutamic acids.

# TRISACCHARIDES

$C_{18}H_{32}O_{16}$ ; sugars yielding three monosaccharides on hydrolysis; classified as reducing and non-reducing. Their structures have been worked out as follows:

- I. Reducing Trisaccharides:  
Mannotriose is glucose-6—1-galactose-6—1-galactoside.  
Rhamninose is galactose-rhamnose-rhamnoside.  
Robinsonose is galactose-rhamnose-rhamnose.  
II. Non-reducing Trisaccharides:  
Melezitose is 1- $\alpha$ -glucose-2- $\beta$ -fructofuranose-6- $\alpha$ -glucoside.  
Gentianose is 2- $\beta$ -fructofuranose-1- $\alpha$ -glucose-6- $\beta$ -glucoside.  
Raffinose is 2- $\beta$ -fructofuranose-1- $\alpha$ -glucose-6- $\alpha$ -galactoside.

# TRITICIN

Fructosan from the honey of *Triticum repens*.

# TRITYL

An abbreviation for the triphenylmethyl group, used particularly in studies of sugar structure.

# TROENSEGAARD'S PYRROLE HYPOTHESIS

Theory of protein structure. Postulates the existence in proteins of a large number of pyrrole rings which hydrolyze at the nitrogen atom, yielding amino acids. This theory cannot account for the optical isomers obtained on hydrolysis, nor is the postulated ring structure sufficiently liable to account for the comparative ease of acid hydrolysis.

# TROPACOCAINE

$C_{15}H_{19}O_2N$ ; benzoyl-pseudotropine; m.p. 49°; an alkaloid of coca leaves, acts like cocaine, less toxic, more transient.

# TROPACOCAINESTERASE

See Enzymes, Non-proteolytic.

# TROPIC ACID

$HO-CH_2-CH(C_6H_5)-COOH$ ; m.p. 117-118°;  $\alpha$ -phenyl- $\beta$ -hydroxypropionic acid; occurs as an ester in atropine and is a mixture of optical isomers.

# TROPIN

See Immunological Phenomena.

# TROPINE

3:6-endo-aminoethyl-cycloheptanone-1;  $C_8H_{15}ON$ ; m.p. 63°, b.p. 233°, a component of atropine and a product of the hydrolysis of atropine.

# TROPINESTERASES

See Enzymes, Non-proteolytic.

# TROPINS

See Opsonins.

**TROPISM**

A turning of an animal resulting from a change in its environment; taxis. See Plant Growth Hormones.

**$\alpha$ -TRUXILLINE**

Isatropylcocaine; cocamine; an alkaloid of the leaves of Erythroxylon Coca, m.p. 80°, which is a heart poison but has no anesthetic action.

**TRUXINE**

An alkaloid,  $C_{21}H_{30}O_4N_2$ , from the seed of Strychnos Ignati and melting at about 250° with decomposition.

**TRYPAN BLUE**

Sodium ditolyldiazobis-8-amino-1-naphthol-3,6-disulfonate; used in trypanosomiasis in cattle, horses, dogs, foot and mouth disease.

**TRYPAN RED**

A reddish-brown powder used subcutaneously or perorally in trypanosomiasis.

**TRYPARSAMIDE**

Na phenylglycinamide-p-arsonate, used as a trypanocide and a mild spirillicide in paresis, tabes, neurosyphilis, etc.

**TRYPSINOGEN**

The crystallizable zymogen occurring in the pancreas from which trypsin is formed by the pancreatic juice.

**TRYPSIN**

A proteolytic enzyme of the pancreatic juice. Hydrolyzes proteins to proteoses and peptones. The crystalline enzyme has an optimum pH of 8-9 with casein. Activated by enterokinase of the small intestine and the pancreas.

**TRYPSINKINASE**

See Trypsin.

**TRYPSIN, TEST FOR**

See Jacoby.

**TRYPTAMINE**

$\beta$ -indole-ethylamine; a poisonous amine formed by bacterial decomposition of tryptophane.

**1-TRYPTOPHANE**

$C_{11}H_{12}O_2N_2$ ;  $\beta$ -Indol- $\alpha$ -amino propionic acid; an indispensable amino acid found in most cell proteins. Shiny hexagonal or rhombic plates, readily sol. hot, slightly sol. cold water, m.p. 289°C (corr.).

**TRYPTOPHANE METABOLISM**

There are two theories, neither of which has been proven beyond question.

(1) Tryptophane goes to indolepyruvic acid, which breaks at the double bond, then recombines, finally yielding kynurenic acid.

(2) Tryptophane, after a several step oxidation, finally yields kynurenin.

The further metabolism is indefinite.

**TRYPTOPHANE TESTS**

See Folin-Looney, Hopkins-Cole, Komm-Buehringer.

**TSCHIRCH REACTION FOR ERGOT**

A red aqueous solution is obtained when 20 cc. ether is poured on 1 gm. ergot, followed by the addition of 10 drops ammonia and 20 cc. water. After swirling and standing for 2 hours, the ether is separated and evaporated, the residue taken up with acetic acid and, after filtering, floated on concentrated sulfuric acid containing a trace of ferric chloride. A blue color forms at the contact zone. The acetic acid layer should show a green fluorescence. Reference: Pharm. Acta. Helv., 1, 69 (1926).

# **TSCHOPP TEST**

A test for determining male sex hormone activity by the capon test.

# **TSCHUGAEV TEST FOR HYDROXYL COMPOUNDS**

The formation of easily identifiable methane by the reaction of methyl magnesium iodide with hydroxyl compounds such as acids, alcohols, oximes and phenols is proof of the presence of the hydroxy group.

Reference: Ber. 35, 3912 (1902); 40, 2023 (1907).

# **TUBERCULOSIS**

A disease caused by *Bacillus tuberculosis* (*Mycobacterium tuberculosis*) which may be acute or chronic, congenital or due to infection, affecting the lungs, liver, nervous system, genital organs, etc. Human and bovine types predominate. Principal forms: (1) acute miliary tuberculosis (2) pulmonary tuberculosis (phthisis, consumption). Sputum diagnoses of several kinds may be made and tuberculin skin tests. The disease can be arrested with great care. Collapse therapy (of the lung) requires the use of artificial pneumothorax.

# **TUBERCULO-STEARIC ACID**

10-methyl stearic acid, isolated from tubercle bacilli.

# **TUBERIN**

A globulin of the potato.

# **TUBOCURARINE**

An alkaloid used as an antitetic.

# **TUMORS, PATHOGENESIS OF**

See Steroids.

# **TUMORS, PLANT**

See Plant Growth Hormones.

# **TURACIN**

Red feather pigment of turaco

bird; a copper salt of uroporphyrin.

# **TURANOSE**

Fructopyranose-6-alpha-glucoside, reducing hydrolytic product of melezitose, m.p. 157°.

See Disaccharides.

# **TURICINE**

Hydroxy-stachydrine; from herb of *Betonica officinalis*; m.p., 260° with decomp. when anhydrous.

# **TURPETHIN**

A glucoside, composition doubtful; a constituent of turpenthum resin; is stated to be a cathartic like jalapin.

# **TUTIN**

A glucoside, either  $C_{17}H_{20}O_7$  or  $C_{15}H_{18}O_6$  from the fruit of *Coriaria ruscifolia*; m.p. 209-212°; pharmacol. action places it in picrotoxin group.

# **TUTOCAINE**

Butamin, p-aminobenzoyl-dimethylamino-1,2-dimethyl propanol hydrochloride; m.p. 212-215°; a local anesthetic.

# **TWITCHELL REAGENT FOR FAT HYDROLYSIS**

Preparation—A mixture of naphthalene and oleic acid is treated with excess concentrated sulfuric acid, excessive temperature rise being avoided by cooling and slow addition of the acid. The crude product formed is dissolved in ether and washed several times with dilute hydrochloric acid and then extracted with water. The aqueous extract is made to contain about 10% naphthalene-stearosulfonic acid, used as a catalyst for ester hydrolysis.

Reference: J.A.C.S. 22, 22 (1900); 29, 566 (1907).

# **TYNDALL BEAM (CONE)**

The band of reflected light that is

visible when a beam of light is passed through a medium containing dispersed particles capable of reflecting the light. Frequently an apparently homogeneous medium is shown to have dispersed particles by the use of this test.

# **TYNDALL METER**

An instrument for measuring the intensity of a Tyndall Cone.

# **TYNDALL PHENOMENON**

See Tyndall Cone.

# **TYPHOID PROPHYLACTIC**

Enteric or typhoid vaccine; bacterial vaccine made from typhoid bacillus; a sterile suspension of killed typhoid bacilli (*Eberthella typhi*) in physiol. sod. chloride soln. or other suitable diluent; used in prophylaxis of typhoid.

# **TYRAMINE OXIDASE**

See Amine Oxidase.

# **TYRAMINE TEST**

See Van-Itallie-Steenhauer.

# **TYRIAN PURPLE**

A bromine containing dye of the shell fish *Murex brandaris*.

# **TYROCIDIN**

A polypeptide of the soil bacillus which is hemolytic and bactericidal in vitro.

# **TYROSAMINE**

See Ergot.

# **TYROSINASE**

An oxidase of potato, bran, fungi, etc., responsible for darkening of cut surface of plants by conversion of tyrosine to melanin.

See Oxyrenin.

# **1-TYROSINE**

$C_9H_{11}O_3N$ ; p-hydroxyphenylalanine; an essential amino acid, and may be a precursor of adrenaline, thyroxine and melanin; m.p. 314-318°, also given as 295°, 1-rotatory, i.p. 5.41.

# **TYROSINE METABOLISM**

See Metabolism, Neubauer's theory of Tyrosine Metabolism, and Dakin's theory of Tyrosine Metabolism.

# **TYROSINE OXIDASE**

See Amine Oxidase.

# **TYROSINE TESTS**

See Denigès, Folin-Denis, Kisch, Landsteiner.

# **TYROSINURIA**

The presence of tyrosine crystals in the urine in cases of destruction of liver tissue, as in acute yellow atrophy.

# **TYROSINOSIS**

An abnormality in which tyrosine metabolism (which see) stops at the formation of p-hydroxyphenylpyruvic acid.

# **TYROSOL**

$\beta$ -(p-hydroxyphenyl)-ethyl-alcohol.

## U

### UKAMBIN

A glucoside from the East African arrow poison of the Wakambas; m.p., 179°; a heart poison.

### ULCER, PEPTIC

See Gastro-Enterology.

### ULCER, STOMACH

See Gastro-Enterology.

### ULEXINE

See Cystisine.

### ULEXOSIDE

A glucoside, from fresh flowers of *Ulex europaeus*; m.p., 247°.

### ULIRON

4 - (4-Aminophenylsulfonamido)-sulfondimethylamide, melting at 193-195°, and used like sulfanilamide.

### ULNA

Inner bone of arm.

### ULTRACENTRIFUGE

A centrifuge, originally developed by The Svedberg, having very high speed, and developing centrifugal forces as high as 7,000,000 times gravity.

See Protein Structure.

### ULTRAFILTRATION

The filtration of a colloidal dispersion through a filter with pores sufficiently fine to retain the dispersed phase, and yet allow the dispersions medium to pass through.

### ULTRAMICRONS

See Submicrons.

### ULTRAMICROSCOPE

A microscope, used largely in the study of colloids, where the source of light is a sharp beam at right angles to the line of vision. What is seen is not the particle itself, but the reflection of light from the particle.

### ULTRASONIC WAVES

Sound waves of a frequency too high to be audible.

### ULTRAVIOLET MICROSCOPY

See Protoplasm.

### ULTRAVIOLET RADIATION

See Growth.

### ULTRAVIOLET RAYS, TEST FOR

See Schall Reagent.

### UMBELLIC ACID

2:4-dihydroxycinnamic acid, found in asafoetida.

### UMBELLIFERONE

$C_9H_6O_3$ ; m.p. 233-234°; 7-hydroxycoumarin; anhydride of umbellic acid, found widely in plants.

### UMBELLULONE

Unsaturated dicyclic ketone of minty odor from *Umbellularia californica*,  $C_{10}H_{14}O$ .

### UMBILICAL CORD

The connection between the foetus and the placenta.

**UNDULANT FEVER**

See Fever Therapy, Brucellosis.

**UNNA-GOLODETZ**

**SULFHYDRYL REACTION**

An aqueous suspension of sulfur is converted to hydrogen sulfide by the reducing action of proteins. The product is identified by its odor and reaction with lead acetate paper.

Reference: *Monatsh. prakt. Dermatol.* 52, 511.

**UNSINARIASIS**

See Ankylostomiasis.

**URACIL**

2:6-dioxytetrahydropyrimidine, m. p. 338° with decomposition; a pyrimidine constituent of plant nucleic acids.

**URACIL, TESTS FOR**

See Johnson-Clapp, Wheeler-Johnson.

**UREA**

Carbamide, Carbonyldiamide; occurs in urine, tissue fluids and blood of all mammals; m.p., 132-33°, sp. gr., 1.335; used in ascites, as test of renal function; externally to promote healing; employed industrially to stabilize explosives and celluloid compositions, in calico printing, mfg. of barbital and allied products.

**UREASE**

The enzyme which splits urea into ammonia and carbon dioxide, probably by way of ammonium carbamate.

**UREA TESTS**

See Moor, Pittarelli, Takeuchi, Weltmann-Barrenscheen.

**URECHITIN**

A glucoside,  $C_{28}H_{42}O_8$ , from leaves of *Urechites suberecta*; a heart poison causing salivation, vomit-

ing, diarrhea, and cardiac paralysis.

**UREMIA**

See Creatine and Creatine Metabolism.

**UREOTELIC**

Pertaining to nitrogen metabolism when the main end product is urea.

**UREOUS ACID**

See Xanthine.

**URETHANE**

Ethyl carbamate,  $NH_2CO-OC_2H_5$ ; m.p. 48-50°; b.p. 182-184°; sp.gr. 1.1; hypnotic antispasmodic, sedative; used internally in convulsions, mild insomnia, also as antidote for certain poisons.

**URETHRA**

The duct leading from the bladder to the exterior.

**URGININ**

A mixture of the two active squill glucosides, Scillaren A and B; used as myocardial stimulant.

**URIC ACID**

$C_5H_4O_3N_4$ ; 2,6,8-trioxypurine, an excretion product of the oxidation of nitrogen compounds, e.g. the nucleic acids.

**URIC ACID TESTS**

See Archetti, Arthaud-Butte, Babo, Benedict, Folin-Denis, Offer, Peronnet-Truhaut.

**URICASE**

An enzyme of animal tissues which catalyzes the oxidation of uric acid by molecular oxygen with the formation of peroxide and allantoin, probably formed via 4:5-glycol uric acid and oxyacetylenediurein carboxylic acid; optimum pH 9.3, attacks other purine compounds; found in liver and kidney.

**URICOLYTIC INDEX**

Ration of allantoin to uric acid



nitrogen; measures presence of uricase.

## URICO-OXIDASE

See Uricase.

## URICOTELIC

Pertaining to nitrogen metabolism when the main end product is uric acid.

## URIDINE

$C_9H_{12}O_6N_4$ ; m.p.  $165^\circ$ ; 3-uracil-d-ribose, a nucleoside of ribonucleic acids of plants.

## URIDYLIC ACID

3-uracyl-3-phosphoriboside, a nucleotide found in ribonucleic acids.

## URINE

A fluid secreted either by simple organisms or higher organisms serving principally as a means of disposal of the products of metabolism especially of nitrogenous compounds. An evolution may be traced from primitive to highly developed kidneys, storage organs or bladders and discharge organs. Human and animal urine often contains suspended material as epithelial cells, casts, pus, mucus, spermatozoa and the like.

Many criteria for human normal urine have been discussed, but none of them are absolute. Cloudiness and turbidity may be due to small amounts of mucus or suspensions of phosphates and carbonates or precipitation of urates on account of cooling. High opacities are more likely to be pathological. Color also varies greatly on account of variable ingestion of fluids and variation in diet. The amount passed normally in 24 hours is averaged at 50 ounces at a specific gravity of 1.020. On the average it is acid, although 3 or 4 hours after meals it normally turns neutral or alkaline, the so-called "alkaline tide" which is sup-

posed to compensate for the secretion of hydrochloric acid in the stomach. The odors vary sometimes on account of food, turpentine producing an odor of violets, asparagus its characteristic odor of asparagine, etc. Numerous substances in the urine are made the subject of tests for pathological change, as urea, creatine, creatinine, albumin, hemoglobin, blood, fat, pus, cystine, glucose, bile, acetone bodies, phosphates, chlorides, sulfates, hippuric acid, non-protein nitrogen, oxalic acid, etc.

## UROBILIN

$C_{33}H_{44}O_8N_4$ ; stercobilin; the brown pigment of the feces; reduction product of bilirubin.

## UROBILINOGEN

Stercobilinogen; a colorless reduction product of urobilin, found in the feces and urine.

## UROBILIN TESTS, IN URINE

See Bogomoloff, Edelmann, Nencki-Sieber.

## UROCANIC ACID

Beta-imidazole-acrylic acid, found in dogs' urine on feeding histidine; also formed by bacterial action on histidine.

## UROCANIC ACID TEST

See Hunter.

## UROCHROME

The chief pigment of urine, a compound of urobilin and a polypeptide.

## UROCHROMOGEN

A colorless precursor of urochrome (q.v.) of which it is a reduction product.

## UROCHROMOGEN TEST

See Schuntermann.

## UROERYTHRIN

A pinkish pigment of the urine present in small amounts except in disease.

## UROLOGY

Urology is that branch of medicine which deals with the genito-urinary tract in the male and the urinary tract in the female.

Urologists date back to the pre-Hippocratic era and were represented by a group known as Lithotomists. These individuals were trained to perform an operation known as lithotomy namely; opening the bladder by way of the perineum. They were capable of performing this operation in thirty seconds. The procedure was passed on from father to son. Though urologists began as surgeons (lithotomists) in the present era (the late nineteenth and early twentieth centuries), they were primarily venereologists and not until the introduction of instruments of precision were they classified as cystoscopists, based on the fact that the cystoscope, first introduced by Max Nitze, was the prime instrument in diagnosing diseases of the urinary tract.

This organic instrument contained a lens system through which the interior of the bladder could be examined. Illumination of the bladder was obtained by a small lamp containing a platinum loop and lit by galvanic current. Ice water had to circulate through the sheath to avoid burning the bladder. With the introduction of the incandescent lamp mechanisms were added to the instrument so as to make it an operating cystoscope, permitting the catheterization of the ureters and the cauterization of tumors, etc.

Nitze soon improved on the lens system and with the aid of a mirror was able to obtain a retrograde view of the bladder neck. Young replaced the mirror and used a four sided prism for retrograde

studies. Albarron added a deflector by means of which the ureteral catheters and electrodes could be directed toward the ureters or bladder tumors.

Before long Reinhold Wappler with the aid of Brown and Buerger remodeled the cystoscope and perfected the operating instrument in use at present.

The instrument of today is composed of three parts, the sheath which has a small lamp fenestra at one end. At the other end there are 2 cocks which control the inflow and outflow of fluids used to distend the bladder. The second part is an obturator used to fill the fenestral opening so as to avoid injury to the urinary canal while introducing the instrument. The third element is the telescope which has the deflector attached to it and channels through which instruments such as catheters, biopsy forceps and fulgurating electrodes can be introduced into the bladder. The infant cystoscope was devised and perfected by Dr. Paul Morgan Butterfield.

About 1922 Doctor Joseph F. McCarthy in conjunction with Reinhold Wappler perfected the fore-oblique system of lenses which gave a forward and downward view (amphitheatre) of the urethra and bladder. This permitted a careful study of the bladder thus bringing the posterior urethra and vesical sphincter into the open. This instrument is called a Pan-endoscope. Not alone has this materially improved cystoscopic visualization of the bladder and urethra but has made operative manipulation more feasible and has made possible the whole procedure of endoscopic resection as carried out today. The catheterization of the ejaculatory

ducts which drain the semen reservoir and vesiculography, was made a simple procedure. The pan-endoscopic system of lenses has been made an integral part of newer instruments used in other specialties for investigating numerous body cavities.

Renal function can be determined by chemical studies of the blood, noting the extent of the nitrogen and creatinine content. It is also important to note the physical properties and chemical findings of the urine. Should one note a discrepancy from the normal, then cystoscopic examination with ureteral catheterization is indicated. One can then isolate or locate the diseased organ.

Separate specimens or urine can be collected from the left and right kidneys. Various dyes such as indigo carmine, phenolsulfonphthalein etc., may be injected intravenously and the appearance at the ureteral catheter can be timed as well as quantitatively estimated. Should hematuria exist, the blood may be seen to appear at either ureteral orifices unless the pathology be in the bladder itself.

The X-ray is of inestimable value to the urologist and especially so since the introduction of the various iodine compounds, originally synthesized by Binz, which are administered intravenously and excreted by the kidneys, thereby delineating the kidney basin, ureters and bladder.

In New York, Reinhold Wappler in 1910, discovered that tissue could be destroyed by a spark produced under water by the high frequency current of Oudine. The active application of this principle by Dr. Edwin Beer to bladder tumors by the use of an insulated

wire passed through the cystoscope added another implement to the urologist's armamentarium. This provided a simple method without open operation of attacking and of curing many hitherto intractable bladder tumors. All tumors do not respond to this treatment, and of these many show cancerous degeneration.

Malignant tumors of the genitourinary tract may be treated by surgery, radiotherapy, fulguration, or any combination of these methods. Radium may be applied directly to the bladder tumor through the cystoscope.

Cancer of the prostate gland is not to be feared. Doctor Charles Huggins in his study of this condition concluded that the endocrine secretion of the testicle was responsible for activating this disease. He advocates bilateral orchidectomy (removal of the testes) which excludes the secretion of the male sex hormone from the body resulting in a regression of the primary tumor and the metastatic lesions.

Here it must be emphasized that sub-serial sectioning according to the method of Doctors S. E. Kramer and J. S. Ritter, of the prostatic tissue removed transurethrally is imperative, in order to detect carcinomatous nests which would otherwise be overlooked.

With the work of Gutman and Gutman of New York who introduced the test for acid phosphatase, we are now able to evaluate the results of castration. Huggins has shown that when the acid phosphatase decreases in a patient who has been operated upon for this disease, one can expect a satisfactory result. It must be kept in mind that this operative procedure is of great value in the adeno-car-

cinoma but of little value in the undifferentiated type carcinoma of the prostate.

The urologist also finds his services applicable to the diagnosis and treatment of the male climacteric sterility and impotence. He finds endocrinological products of use here, as in mild cases of benign hypertrophy of the prostate, and perhaps even in carcinoma of the prostate. Various endocrinologic dysfunctions, as for example, masculinization of the female from adrenal tumors, also fall within his field.

Pyelonephritis, cystitis and combined upper and lower urinary tract infections may be treated with ketogenic diets and urinary antiseptics, such as mandelic acid and methenamine. Their effectiveness, however, varies with the invading organism and the pH of the urine. Chemotherapy with the sulfonamides has been found of inestimable value but the administration of these drugs requires great caution because of their toxic effects both systemic, such as anemia and agranulocytosis, and local crystalline deposit, stone formation, and hematuria.

Gonorrhea has always been one of the commonest ailments seen by the urologist. It attacks a large percentage of the male population, is transmissible with great ease, and if untreated, or unsuccessfully treated, may cause severe invalidism, not only in the male but particularly in the female patient. The sulfa drugs have, in the treatment of this venereal disease, found an extraordinary success, in that the morbidity, duration of the infection, and incidence of complications have been markedly reduced. The prophylaxis of gonorrhea is, of course,

of the utmost importance.

Much has been written relative to calculi of the urinary tract. This is perhaps the most perplexing pathological entity. The removal of the primary calculus, or stone, is simple. However attempts to avoid the recurrence of these stones is of first consideration. Here the biochemist is of great importance; not alone to determine the composition of the calculus but in the selection of the proper diet to avoid the reformation of the calculus. Vitamin A deficiency has been advanced as one of the important causes of stone formation. However, infection and stasis are two of the prime factors.

It is important that at the time of operation the entire calculus be removed for any remaining fragments may result in early deposits and a reformation of the stone.

One of the greatest single figures in modern urology is Dr. Hugh Hampton Young, of Johns Hopkins Hospital. Among the innumerable contributions which Dr. Young has made to his branch of medicine are the origination of surgical operations and the design of many ingenious instruments necessary for the development of his operative and non-operative cystoscopic techniques. He advocated the perineal approach for the removal of the enlarged prostate gland and also performed the first radical operation for carcinoma of the prostate by removing the entire prostate in its capsule with a contiguous portion of the bladder. He also developed the "cold punch" operation for median bar obstruction of the vesical neck. This was first performed in 1909 under local anesthesia and it obviated the necessity for an



external incision for the removal of comparatively small amounts of tissue. Bottini antedated Young in using an actual cautery to remove obstruction at the bladder neck.

About 1925, Reinhold Wappler with Dr. Maximilian Stern developed the resectoscope, Mr. Wappler having perfected an electrical modality to cut tissue under water. Davis of North Carolina improved on the Stern instrument. Doctor Joseph F. McCarthy working in conjunction with Reinhold Wappler developed the present resectoscope that bears his name. In this the fore-oblique telescope plays an important part.

Transurethral resection, as this operative procedure is termed, is employed in the treatment of prostatic obstruction to varying degrees. That is, in the middle West and far West, the urologists practice resection exclusively and as one travels East, this procedure is limited to fibrotic prostate, the small and median lobe hypertrophies and in cancer of the prostate gland.

Urology, probably the most advanced single specialty of medicine, has attracted investigative minds that daily contribute newer improved modalities for the relief of mankind infirmities. Beginning as the speediest of surgeons lagging back into the field of venereology it is now rapidly recapturing the front line trenches of modern medicine.

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## URONIC ACIDS

Acids obtained by the oxidation of a primary alcohol group of a sugar without a change of the aldehyde group, e.g. glucuronic acid.

## UROPORPHYRIN

$C_{40}H_{38}O_{16}N_4$ ; a porphyrin derivative found in the urine of people with congenital porphyrinuria.

## UROPTERIN(E)

A constituent of human urine probably identical with xanthopterin(e), q.v.

## UROROSEIN

The precursor of the red coloring matter of certain pathological urine, probably indole acetic acid, which turns red with conc. HCl and Na nitrite.

## URORUBIN

A pathological red urine pigment.

## UROTROPIN

See Hexamethylenetetramine.

## URSODESCHOLIC ACID

A bile acid, m.p.  $198^\circ$ , found in the bear. It is a dihydroxycholeic acid,  $C_{24}H_{40}O_4$ .

## URSOLIC ACID

See Urson, Prunol, Malolic Acid;  $C_{30}H_{48}O_8$ ; found in leaves of apples and pears; m.p.  $285^\circ$ .

## URSON

See Ursolic Acid.

## UTERUS

Womb; the organ protecting and nourishing the fetus.

## URTICARIA

See Itching.

## UVA URSI

Bearberry; dried leaves of *Arctostaphylos Uva-ursi*; used as diuretic, astringent.

## UVEAL TRACT

See Eye, Biochemistry of.

## UZARIN

A glucoside,  $C_{75}H_{108}O_{30} \cdot 9H_2O$ , from uzara root; m.p.,  $200-210^\circ$ .  
See Digitalis.

## V

### VACCENIC ACID

An isomer of oleic acid with double bond at 7th and 8th carbon atom.

### VACCINE BRUCELLA MELITENSIS

Suspension of killed *B. melitensis* (*B. abortus*) in physiol. soln. sod. chloride; used in undulant fever.

### VACCINIIN

A glucoside, 6-benzoyl-d-glucose; from various species of *Vaccinium* berries; m.p. 104-6°.

### VACUOLES, FOOD

See Digestion.

### VAGOTONIN

A supposed hormone which controls the excitability of the vagal nerve center; affects heart and general blood pressure.

### VAGUS

See Respiration.

### VALDIVIN

A glucosidal amaroid, from fruit of *Simaba valdivia*, melting at 230° when anhydrous; claimed to be identical with cedrin by some and more toxic than cedrin by others.

### VALENTA REAGENT FOR FATS

Depending upon their source, fats and fatty oils produce clear solutions with glacial acetic acid at various temperatures.

Reference: Zeit. anal. Chem. 24, 295 (1895). Analyst 1918, 87.

### VALERIAN

Dried rhizome and roots of *Valeriana officinalis* L. Valerianaceae; contains valerine, chatinine (alkaloids); used as sedative, antispasmodic.

### VALERIANIC ACID

Four structural isomerides are possible and known: (1) n-valeric acid, b.p. 185°; (2) isovaleric acid,  $(\text{CH}_3)_2\text{CHCH}_2\text{COOH}$ , b.p. 175°; (3) methyl ethyl acetic acid, b.p. 177°; (4) trimethyl acetic acid (pivalic acid) b.p. 164°. Isovaleric acid occurs in the free state in many plants, e.g. valerian root. The acidum valerianicum of pharmacy is isovaleric acid with some methyl ethyl acetic acid.

### 1-VALINE

Alpha-amino-isovaleric acid, m.p. 93-96°, amino acid, d-form in nature, found in plant seedling protein and others.

### VALLARIN

A glucoside from an undetermined *Valaris* species; in frog 2 mgm. causes miosis, paralysis, dyspnea, and death.

### VALONIA

An alga much used in permeability



studies because of its large cells.  
See Permeability, Protoplasm.

**VALTON TEST FOR METHYLAMINE IN PRESENCE OF AMMONIA**

The test solution, mixed with 30 cc. 2N sodium hydroxide is placed in a flask and diluted with water to 80 cc. Using a Kjeldahl apparatus, the mixture is distilled into 10 cc. of a 0.5% alcoholic solution of 2,4-dinitrochlorobenzene. After distilling 10 cc., the mixture is allowed to stand for 20 hours; a crystalline precipitate of dinitromethylaniline is formed. Reference: J. Chem. Soc. 127, 40 (1925).

**VANADIUM CHROMOGEN**

A respiratory pigment of the blood of Tunicata such as Ascidia, containing about 10% of vanadium in the form of various oxides combined with a pyrrol containing protein.

**VAN DEEN REACTION FOR BLOOD**

Treatment of dilute blood solution with several drops of tincture of guaiac resin and red (ozonized) turpentine oil yields a blue color.

Reference: Arch. f.d. h lland. Beitr. zur Naturwiss. u. Helik., Utrecht, III, 228 (1861-64). Gazz. chim. ital. 10, 213 (1880). Analyst 38, 186. J.A.M.A. 1907, No. 23. M nch. med Wochschr. 1908, 2504; 1910, 1085. J. pharm. chim. 22, 52 (1920).

**VAN den BERGH TEST FOR BILIRUBIN IN BLOOD**

One part of blood serum is mixed with 2 parts 95% alcohol, the precipitated albumin is removed by

filtering or centrifuging and, to the clear colution,  $\frac{1}{4}$  its volume of Ehrlich's diazo reagent is added; a red color is obtained. Reference: Presse m d. 1921, 441. Biochem. J. (1), 26, 165 (1932).

**VAN der HAAR REAGENT FOR d-GALACTOSE**

d-Galactose gives a crystalline hydrazone with o-tolyhydrazine, in contrast to other sugars.

Reference: Rec. trav. chim. 37, 108 (1917).

**VANILLIN**

Methylprotocatechuic aldehyde; Vanillic aldehyde; 3-Methoxy-4-hydroxybenzaldehyde; m.p., 80-81 ; occurs in vanilla, potato parings, Siam benzoin etc.; synthesis from eugenol or guaiacol; used as flavoring agent in confectionery, foods, beverages; also as reagent in anal. chemistry.

**VAN ITALLIE-STEENHAUER MICROCHEMICAL REACTIONS FOR DIFFERENTIATING TYRAMINE AND HISTAMINE**

The formation of the following double salts serves to distinguish easily between the two bases: chloroplatinate, iodobismuthate, iodoplatinate, phosphotungstate, picrate and silicotungstate.

Reference: Mikrochemie 3, 65 (1925).

**VAN SLYKE'S METHOD**

A method for determining amino nitrogen of proteins or amino acids by titration with nitrous acid and the liberation of nitrogen gas.

**VAN SLYKE'S METHOD OF PROTEIN ANALYSIS**

A method which combines the Hausmann procedure with amino nitrogen determinations, etc., to

determine individual amino acids.  
References: Van Slyke, Jour. Biol. Chem. 10, 15-55; 22, 281-5; 23, 411; Gortner and Sandstrom, Jour. Am. Chem. Soc., 47, 1663-1671.

#### VAN URK REACTION

See Ergot.

#### VAN ZIJP REACTION FOR CHOLESTEROL

A thin layer of cholesterol, obtained by evaporation of a chloroform solution, gives blue or bluish-black crystals upon 1-4 hours exposure to vapors of concentrated hydriodic acid containing iodine. Ergosterol and phytosterols do not react, nor does cholesterol in the presence of more than 5% phytosterols.

Reference: Pharm. Weekblad 70, 775 (1933).

#### VARIOLA

See Smallpox.

#### VASCULAR

Pertaining to vessels.

#### VASOPRESSIN

See Pituitrin.

#### VELICOGNA TEST FOR ADRENALINE

A cardinal-red color is developed in 5-10 minutes when a mixture of 3 cc. 1% solution of phenol in 50% alcohol, 0.6 cc. saturated potassium iodate solution, and 0.1 cc. saturated sulfanilic acid solution is heated on a water bath. The addition of a trace of adrenaline results in a more rapid development of color; sensitivity—1:12 million.

Reference: Compt. rend. soc. biol. 115, 140 (1934).

#### VELLARIN

An amaroid from leaves and root

of *Hydrocotyle asiatica*, and used in leprosy and syphilis.

#### VELLOSINE

An alkaloid from bark of *Geissospermum Vellosii* Allem., Apocynaceae; m.p. 189°; very toxic, physiol. action corresponding with that of brucine.

#### VELLUS

See Hair.

#### VENEREOLOGY

See Urology.

#### VENTRAL

Frontal of abdominal.

#### VENTRICLE

Cavity (of heart, brain).

#### VENTRICULIN

A commercial name for defatted, desiccated hog stomach used in the treatment of anemia.

#### VERATRIC ACID

Dimethyl-protocatechuic acid; 3, 4-Dimethoxybenzoic acid; obtained synthetically and from seed of *Sabadilla officinalis*; m.p., 180-181° when anhydr., sublimes in rhombic crystals.

#### VERATRIDINE

An alkaloid,  $C_{36}H_{51}O_{11}N$ ; from seed of *Sabadilla officinalis* and from rhizome of *Veratrum album*; m.p. 180°; is hydrolyzed into amorphous cevine (verine) and veratric acid.

#### VERATRINE ALKALOIDS

A group of alkaloids of which the outstanding ones are veratrine, or cevadine, and protoveratrine, occurring in various hellebores; soften pulse and lower blood pressure; emetic.

#### VERBACOSE

Isomer of raffinose, m.p. 219°.

#### VERBENALIN

A glucoside,  $C_{17}H_{25}O_{10}$ ; from

whole plant, particularly the flowers of *Verbena Officinalis*; m.p., 178°; hastens blood coagulation and is a uterine contractor.

# VERBENONE

An unsaturated ketone in Spanish verbena oil found in d- and l-forms.

# VERDOHEMATIN

Bile pigment hematin.

# VERDOHEMOCHROMOGEN

Bile pigment hematin-protein.

# VERDOHEMOGLOBIN

Choleglobin; pseudohemoglobin; a green chromoprotein obtainable from hemoglobin by hydrogen peroxide oxidation, contains verdohematin, a biliverdin-iron complex or prosthetic group.

# VERNONIN

$C_{10}H_{24}O_7$ ; a glucosidal amaroid of the root of *Veronia nigrifolia* Oliv., Compositae, which is a heart poison less toxic than digitalin.

# VERTEBRATA

A subphylum of the phylum Chordata; characterized by having a sectional bony column running down the center of the dorsal side of the animal.

# VERTIGO

Dizziness; giddiness; a disorder of the sense of equilibrium.

# VERUCCA

See Wart.

# VESICLE

Cavity or sac.

# VESICULOGRAPHY

See Urology.

# VESTLIN TEST FOR SAPONIN

A 1:125000 solution of Gypsophila saponin hemolyzes horse blood at 37-42°; a 1:1 million solution produces only slight hemolysis.

Reference: Biochem. Zeit. 144, 9 (1924).

# VIABLE COUNT

A method of counting bacteria by diluting, plating and counting colonies.

# VIBRIO BACILLUS

See Microbiology.

# VIBURNUM PRUNIFOLIUM

Dried root bark of viburnum prunifolium containing viburnin, bitter resin, tannin and certain organic acids; is a supposed uterine sedative; internally for after-pains, habitual abortion, menorrhagia.

# VICIANIN

$C_{19}H_{25}O_{10}N$ ; m.p. 147-148°; a glycoside of the seeds of *Vicia angustifolia* yielding vicianose and HCN by the action of the enzyme vicianase.

# VICIANOSE

Glucose-6-beta-1-arabinoside, a constituent of the glycosides, vicianin, violutin and gein; m.p. 210°, unfermentable.

# VICILIN

A globulin of various legumes.

# VICINE

$C_{10}H_{16}O_7N_4 \cdot 2H_2O$ ; m.p. 239-240°; 3-divicine-d-glucoside, a nucleoside found free in plant tissues, e.g. seed of *Vicia sativa*.

# VIEHOVER TEST FOR MARIHUANA

One-third or more of the wrapless cigarette or at least 0.1 gm. of the weed is placed in a stoppered flask and treated with 3 cc. of isopropyl (or any common) alcohol containing 0.05% sodium hydroxide and 0.05 gm. activated charcoal. An immediate color change to pinkish, deepening after a short time, is positive.

After evaporation, the residue dissolves in concentrated ammonia with an orange-red color and in acetone with violet to blue-violet color.

Reference: Am. J. Pharm. 109, 589 (1937).

## VILLI

See Gastro-Enterology.

## VILLIKININ

A substance stimulating motility of the villi and secretion of the intestinal mucosa, found also in the Bios fraction of yeast.

## VILLOSIN

A glucoside from root bark of *Rubus villosus*, melting at 173-175°.

## VILTER-SPIES-MATHEWS REACTION FOR NICOTINIC ACID AND NICOTINAMIDE

A mixture of the acid with twice its weight of 2,4-dinitrochlorobenzene is melted over a flame and treated with alcoholic potassium hydroxide; a brilliant purple color is obtained even with 0.3 mg. of acid.

To test urine, 15 cc. are boiled with 0.1-0.3 gm. decolorizing charcoal, filtering and evaporating 3 cc. to dryness at 80-100°. One cc. of 1% alcoholic 2,4-dinitrochlorobenzene is added, kept at room temperature for 1-3 hours, again evaporated to dryness and heated at 105° for 10 minutes. After cooling to 25°, add 10 cc. of a clear cold 0.1% alcoholic potassium hydroxide solution. Nicotinamide gives a red color, nicotinic acid a clear purple color.

Reference: J. Biol. Chem. 125, 85 (1938).

## VINCENT'S ANGINA

Trench mouth; an ulcerative dis-

ease of the mouth due possibly to a spirochaete at least as a secondary infection. It may resemble diphtheria. Strong oxidizing agents or arsphenamine derivatives are used persistently.

## VINCETOXIN

A glucoside; m.p., 132° with decomp.; from root of *Vincetoxicum officinale*.

## VIOFORM

See Chemotherapy.

## VIOLANIN

A chromo-glucoside,  $C_{27}H_{28}O_{15}$ , from flowers of *viola tricolor*.

## VIOLAQUERCITRIN

See Rutin.

## VIOLASCEIN

A bacterial pigment.

## VIOLAXANTHIN

$C_{40}H_{56}O_4$ , a carotenoid pigment, present in ester form in *viola* petals, m.p. 208°.

## VIOLUTIN

$C_{19}H_{28}O_{12}$ ; m.p. 169-172°; violutinside; a glucoside from *Viola cornuta* which on hydrolysis yields methyl salicylate, l-arabinose and d-glucose.

## VIOLUTISIDE

See Violutin.

## VIOSTEROL

A commercial name for irradiated ergosterol used in the prophylaxis and treatment of rickets and infantile tetany.

## VIRUSES AND GENES

See Genetics.

## VIRUS PROTEINS

See Filtrable Viruses.

## VISCOSITY

The internal friction of a liquid; the resistance to shear or flow. The unit of viscosity is the poise.

**VISCOSITY, PROTOPLASMIC**

See Protoplasm.

**VISIBILITY, MICROSCOPIC**

See Protoplasm.

**VISUAL PURPLE**

Rhodopsin; reddish purple pigment of retinal rods.

See also Eye, Biochemistry of.

**VISUAL YELLOW**

The compound formed from visual purple (rhodopsin) by light; actually yellow retinene and a protein.

**VITAIDS**

A term used by Lepeshkin (1936) for the continuous phases of living protoplasm, which disintegrate on death.

**VITAMIN A**

A growth promoting organic substance, lack of which leads to keratinization of the epithelial tissues, with ensuing bacterial invasion. Synthesized in liver cells from  $\alpha$ - and  $\beta$ -carotene; found in fish liver oils, egg yolk, etc. 70 Kg. adult needs 1400-2000 U.S.P. units, and 2-4000 is desirable. No absorption spectra bands in visible, broad region in ultraviolet light, with maximum at 328 mm. in  $\text{CHCl}_3$ . Stored to varying extent in animals, largely in liver. Absorbed as an ester from the thoracic duct.

Forms a blue compound with  $\text{SbCl}_3$ , max. abs. band at 620 mm.

**VITAMIN A<sub>2</sub>**

Another naturally occurring form of Vitamin A. The principal vitamin A of fresh water fish, and found to a lesser extent in the liver oils of other fish. Differs spectroscopically from vitamin A. Probably physiologically active in mammals.

**VITAMIN A, CRYSTALLINE**

$\text{C}_{20}\text{H}_{30}\text{O}$ ; yellow prisms, m.p. 63-

64°, from shark liver, cod liver, jewfish liver and halibut viscera; provisional potency 4,300,000 International units.

Reference: James G. Baxter & C. D. Robeson, Jour. Am. Chem. Soc. 64, 2411-2416 (1942).

**VITAMIN A**

**INTERNATIONAL UNIT**

The growth promoting activity in rats of 0.0006 mg. of a standard crystalline  $\beta$ -carotene.

**VITAMIN A TESTS**

See Carr-Price, Chevallier-Choron, Fearon, Pacini-Taras, Rosenheim-Drummond, Rosenthal-Erdelyi, Wait Reaction.

**VITAMIN B COMPLEX**

A name for the mixture of water soluble vitamin factors found together in yeast and elsewhere, which have been separated in at least 9 components. The nomenclature is now in a highly fluid state. See individual types as  $\text{B}_1$ ,  $\text{B}_2$ , etc.

See also Hair.

**VITAMIN B<sub>1</sub>**

See Thiamin Chloride.

**VITAMIN B<sub>1</sub> EFFECTS**

The administration of the vitamin has a sparing action on fat, it aids in the conversion of carbohydrates via pyruvic acid to fat (rat, pigeon) and accelerates fatty liver development in rats and chicks on low choline.

**VITAMIN B<sub>1</sub> TESTS**

See Barger-Berger-Todd (Thiochrome), Jansen, Kinnersley-Peters, Naiman, Prebula-McCollum, Raybin, Tauber, Willstaedt.

**VITAMIN B<sub>2</sub>**

See Riboflavin.



**VITAMIN B<sub>3</sub>**

Obsolescent name for a thermostable member of the vitamin B complex necessary for pigeon growth and weight increase; found in brewer's yeast, whole grains, liver and malt.

**VITAMIN B<sub>4</sub>**

Obsolescent term for a factor of vitamin B complex supposedly necessary for the growth of rats.

**VITAMIN B<sub>5</sub>**

An obsolescent name for the heat stable component of vitamin B complex which prevents the loss of weight in pigeons. Vitamin B<sub>5</sub>, however, is necessary for a gain of weight.

**VITAMIN B<sub>6</sub>**

See Pyridoxin(e).

**VITAMIN C**

See Ascorbic Acid, also Wound Healing.

**VITAMIN D**

There are possibly 9 forms, including calciferol, 2,2-dihydroxycalciferol, irradiation products of 7-dehydrocholesterol, 7-hydroxycholesterol, 7-dehydrositosterol, their isomers, cholesterolene sulfonic acid, an ergosterol derivative with alkyl nitrites and alkyl amines, natural forms not quite identified.

See Calciferol and Vitamins D<sub>1</sub> to D<sub>4</sub>.

**VITAMIN D<sub>1</sub>**

A molecular compound of calciferol (vitamin D<sub>2</sub>) and lumisterol.

**VITAMIN D<sub>2</sub>**

The name used for calciferol especially in German literature, C<sub>28</sub>H<sub>44</sub>O, m.p. 115-117°; 1 milligram equals 40,000 international units.

**VITAMIN D<sub>3</sub>**

The irradiation product of dehydrocholesterol, found in fish liver oils and in the skin; C<sub>27</sub>H<sub>44</sub>O, m.p. 82-4°.

**VITAMIN D<sub>4</sub>**

The irradiation product of 22-dihydroergosterol.

**VITAMIN D TESTS**

See Halden, Steigmann, Stoeltzner, Wait Reaction.

**VITAMIN E**

See α-Tocopherol.

**VITAMIN G**

See Riboflavin.

**VITAMIN H**

See Vitamin B<sub>6</sub>, Biotin.

**VITAMIN K<sub>1</sub>**

2-methyl-3-phytyl-1,4-naphthoquinone; alaphylloquinone; a yellow colored substance found in plant tissues and vegetable oils, promoting blood coagulation; also synthesized by bacteria.

**VITAMIN K<sub>2</sub>**

A 2-methyl-1,4-naphthoquinone derivative with a longer unsaturated side chain than vitamin K<sub>1</sub>, which has similar action.

**VITAMIN K UNIT**

The equivalent of 1 gamma of 2-methyl-1,4-naphthoquinone, or 3 and 1/3 gamma of vitamin K<sub>1</sub>.

**VITAMIN P**

A factor found in lemon juice, the lack of which results in hemorrhages of the mucous membranes and severe constitutional disturbances. It may be a mixture of the flavones, hesperidin and eriodictol.

**VITAMINS**

See also Metabolism, Teeth, Biochemistry of, Growth.



**VITAMINS AND MENTAL STATES**

See Psychiatry Biochemistry of.

**VITELLIN**

Ovovitellin; a phosphoprotein of egg yolk, yellow.

**VITELLINE BODY**

Yolk nucleus.

**VITELLUS**

Yolk, vitellin.

**VITREOUS HUMOR**

See Eye, Biochemistry of.

**VIVIDIFFUSION**

A technic used for applying diffusion and ultrafiltration to the blood stream of a living animal. It consists of passing the carotid arterial blood, after addition of an anticoagulant, through collodion tubes suspended in water or physiological salt solution, and then back to the femoral vein.

**VIVIPARITY**

The carrying of the young till birth in the maternal body.

**VOISENET'S REACTION (1905)**

A test for proteins, supposedly due to the presence of tryptophane. The protein solution is treated with a trace of formaldehyde. On adding hydrochloric acid with a bit of nitrous acid to this, a violet color is developed.

**VOLEMITOL**

Sedoheptitol; a 7 carbon sugar alcohol of Lactarius volemus.

**VON GRAEFE'S SIGN**

See Goiter.

**VOSGES-PROSKAUER DIACETYL REACTION FOR PROTEINS**

Bacteria in a culture form acetyl-methylcarbinol from the sugar. The test is based on the oxidation of the carbinol to diacetyl. In the presence of alkali, proteins and diacetyl form a violet-red product with a green fluorescence. The aerogenes group, which gives the reaction, may thus be distinguished from the colon group.

Reference: Zeit. Hyg. 28, 20.

**VOTOCEK TEST FOR KETOSES**

A drop of test solution is added to a mixture of 2 cc. glacial acid, a small amount of carbazole and 1 drop fuming hydrochloric acid and heated on a water bath for 10 minutes; a cherry-red color is obtained.

Reference: Chem. Listy 5, 14 (1911).

**VULPIAN REACTION,**

The green color formed by reaction of adrenaline with ferric chloride in slightly acid solution.

**UZIN DIHYDROCHLORIDE**

Isooctylhydrocupreine dihydrochloride,  $C_{19}H_{23}ON_2 \cdot OC_8H_{17} \cdot 2HCl \cdot 2H_2O$ ; used as powerful bactericide and externally for boils, abscesses, carbuncles, and infected wounds.

## W

### WAGENAAR REACTION FOR CAFFEINE

Deep brown crystals are obtained when a caffeine solution is treated with cesium chloride, a drop of potassium iodide solution and a drop of sulfuric acid.

Reference: *Mikrochemie* 13, 145 (1933).

### WAGENAAR TEST FOR ACETONE IN URINE

A mixture of 10 cc. urine, 10 drops glacial acetic acid, 10 drops 20% tartaric acid solution, 20 drops fresh 20% sodium nitroprusside solution is layered with ammonia. A distinct purple ring is produced, even with as little as 0.5 mg. acetone. The test is specific.

Reference: *Pharm. Weekblad* 55, 57 (1918).

### WAGENAAR TEST FOR DISTINGUISHING CITRIC, OXALIC AND TARTARIC ACIDS

A mixture of a few drops of ferric chloride solution and 20 drops of water is treated with 0.3 gm. aminopyrine and 0.03 gm. resorcinol; 0.05 gm. of the acid and 3 cc. concentrated sulfuric acid are added and heated over a small flame. Citric acid gives a yellowish-brown color; oxalic acid a

dark green color changing to pale green; tartaric acid gives deep red changing to raspberry.

Reference: *Schweiz. Apoth.-Ztg.* 64, 177 (1926).

### WAGENAAR TESTS FOR FRUCTOSE AND SUCROSE IN LACTOSE

A suspension of a few mg. of sugar in a drop of a 2% glycerin solution of  $\alpha$ -naphthol is treated with a drop of concentrated sulfuric acid. Fructose gives an immediate blue color. A suspension of lactose in a drop of the glycerin solution of  $\alpha$ -naphthol is treated with a drop of concentrated sulfuric acid and stirred with a platinum wire. Sucrose forms a blue-violet color within 10 minutes.

Reference: *Pharm. Weekblad* 70, 1029 (1933); 71, 281 (1934).

### WAGENAAR TEST FOR HYDROCHLORIC ACID IN GASTRIC CONTENTS

A solution of 0.2 gm. of vanillin in 5 cc. of boiling water is crystallized by cooling. One drop of the crystalline suspension is evaporated on a watch glass, treated with 1 drop of gastric juice and evaporated at a low temperature; a violet zone forms if the hydrochloric acid contents exceeds 0.0015N. Of the organic

acids, only oxalic interferes.

Reference: Pharm. Weekblad 1935, 837.

# WAIT REACTION FOR VITAMINS A, C AND D

Vitamins A and C give a blue color with a 1% acetic acid solution of phosphomolybdic acid, vitamin D gives a green color. Substances containing both vitamins and D give a green color first, followed by the characteristic blue of vitamin A.

Reference: Pharm. Zentralhalle 78, 237 (1937).

# WARBURG-CHRISTIAN FLAVOPROTEIN

A flavoprotein enzyme from bottom yeast, m.w. about 70,000; promotes the reaction of hexosemonophosphate and coenzyme II which forms phosphohexonate and reduced coenzyme II by reoxidizing the reduced coenzyme and itself being reduced; the reduced flavoprotein is oxidized by molecular oxygen with the formation of peroxide.

# WARBURG'S RESPIRATORY FERMENT

An intracellular, structure-linked catalyst present in all aerobic cells, catalyzing the reaction of cytochrome with oxygen. Consists of a pteohemin in combination with a high-molecular protein; the ferri form reacts with HCN, the ferro form binds CO in a reversible, photodissociable manner. .K.G.St.

# WART

Verucca; a virus infection showing as a thickened callosity. Warts may be removed by trichloroacetic acid, salicylic acid, freezing and cauterizing, electrodesiccation by sparking, X-ray therapy and even by internal administration of arsenic.

# WASER TEST FOR AMINO ACIDS

A few cc. of solution (or a few mg. of solid) are boiled with 3-4 cc. of 10% sodium carbonate solution and treated with a pinch of p-nitrobenzoyl chloride;  $\alpha$ -amino acids form a dark wine-red to violet-blue color. By boiling 0.5-1 cc. of solution with 1 cc. of pyridine and a crystal of the p-nitro compound and slowly adding sodium carbonate solution, a similar color may be obtained. Reference: Mitt. Lebensm. Hyg. 20, 260 (1929).

# WASSERMAN REACTION

This reaction is an application of the complement fixation method (q.v.) which employs as antigen a non-specific lipid, usually the alcoholic extract of beef heart.

K. L.

# WATER INTOXICATION

Convulsions produced by forcing very large amounts of water due to effect on brain, edema, loss of chloride and alkalosis.

# WATER METABOLISM

See Creatine and Creatinine Metabolism.

# WATER PURITY

See Microbiology.

# WATER-SOLUBLE B

A name employed in 1916 by McCollum for thiamin. Fell into disuse after 1920.

# WATS-GHOSH TEST FOR ATEBRIN IN URINE

A mixture of 100 cc. of urine and 10 gm. of potassium carbonate is shaken with 20 cc. amyl alcohol. The alcohol layer is decanted and washed with a saturated aqueous solution of potassium carbonate; atebtrin gives a yellow color and the passage of a beam

of light through the liquid against a black background gives a distinct green fluorescence. Sensitivity—1:10 million.

Reference: Records Malaria Survey India 4, 367 (1934).

## WAXES

Solid or liquid esters of the higher fatty acids with mono- and sometimes dihydroxy-alcohols or with sterols. They frequently appear as protective coatings in the plant and animal kingdoms.

## WELTMANN-BARRENSCHEEN TEST FOR UREA

An aqueous solution of urea gives, with Ehrlich's aldehyde reagent, an intense yellowish-green color.

Serum, dealbuminated with trichloroacetic acid, is filtered and 1 cc. of filtrate is treated with 4 drops of Ehrlich's reagent; when the residual nitrogen value exceeds 36-40 mg., a yellow-green color develops. Sensitivity of reaction corresponds to pathological threshold value.

Reference: Wiener med. Wochschr, 1922, 766.

## WENDER REACTIONS FOR DIASTASE

Five cc. of 1:1000 diastase solution are mixed with 1 cc. dilute hydrogen peroxide and 10 drops of one of the following. (a) Alcoholic guaiac resin solution and hydrogen peroxide, intense blue color; (b) guaiac wood tincture and hydrogen peroxide, dark blue color; (c) pyrogallol solution and peroxide, orange-red color; (d) naphthol solution and peroxide, violet-blue; (e) dilute p-phenylene diamine hydrochloride solution and peroxide, violet-brown.

Reference: Apoth.-Ztg. 1903, 471.

## WEYL'S REACTION

The reaction of creatinine with sodium nitroprusside to give a red color which changes to yellow.

## WHARTON'S JELLY

A preparation of the umbilical cord.

## WHEELER-JOHNSON REACTION FOR URACIL, CYTOSINE AND ISOCYTOSINE

Bromine water is added to uracil or cytosine until a yellow color is obtained; excess bromine is removed by bubbling in air followed by barium hydroxide solution. A purple-red to violet color or precipitate is formed. Isocytosine gives a blue color.

Reference: J. Biol. Chem. 1907, 183.

## WHISKEY

A liquid produced by distillation of the fermented mash of malted cereal grains and which has been stored in wood containers for not less than 4 years; contains 0.05-0.16% acid calculated as acetic acid and 0.038-0.15% esters as ethyl acetate; absolute alcohol is 47-53% by volume; is stated to have intoxicating effects when taken internally, attacking the central nervous system.

## WHITEHORN REAGENT FOR AMINES

Organic bases are taken up from aqueous solutions and solutions in organic solvents by Permutit, a sodium aluminum silicate.

Reference: J. Biol. Chem. 56, 751 (1923).

## WIDMARK & LARSSON'S TITRATION

Electrometric titration of the carbonyl group in amino acids or proteins.

# WIELAND THEORY

See Carbohydrate and Fat Catabolism.

# WIJS SOLUTION FOR IODINE NUMBER

A solution of 13 gm. iodine in 1 liter of 95% acetic acid is treated with hydrogen chloride-free chlorine gas until the titer of the solution is doubled. The solution changes only very slightly in titer.

Since the solution contains 7.8 gm. iodine trichloride and 8.5 gm. iodine per liter, the solution may be prepared by dissolving these substances.

Reference: Ber. 1898, 750. Chem.-Ztg. 1914, 1111.

# WILD CHERRY

Wild black cherry bark; from *Prunus serotina*, Ehrhart, Rosaceae; contains prunasin, glucose, hydrocyanic acid and other organic components; used in form of syrup as vehicle for cough medicine.

# WILLSTAEDT REACTION FOR VITAMIN B<sub>1</sub>

2,4-dichlorobenzenediazonium chloride reacts with the vitamin forming a yellow-red color, quantitatively extracted with ether. The dye is separated from other dyes by filtration through a column of calcium hydroxide, followed by elution of the adsorbent with alcohol.

Reference: Naturwissenschaften 25, 682 (1937).

# WINDAUS REACTION FOR CHOLESTEROL

I. A solution of cholesterol in the least volume of ether is treated with bromine in glacial acetic acid until distinctly yellow-brown. Cholesterol dibromide,

melting at 123-124°, precipitates immediately.

II. Cholesterol, in alcoholic solution, is precipitated almost quantitatively by an alcoholic solution of digitonin in the form of an equimolecular complex.

Reference: Chem.-Ztg. 1906, 1011. Ber. 1909, 238. Zeit. physiol. Chem. 1910. Arch. Pharm. 1911, 432. Dermatol. Wochschr. 97, 1651 (1933).

# WINKLER REACTIONS FOR DIFFERENTIATING THEOBROMINE, THEOPHYLLINE AND CAFFEINE

I. 0.1 gm. theophylline is shaken with a mixture of 2 drops 1:100 phenolphthalein, 1 drop of 0.1N sodium hydroxide and 5 cc. water. The solution is decolorized immediately while caffeine and theobromine do not react.

II. One cc. of ammonia will dissolve 0.1 gm. theophylline, while the other two will not dissolve. Reference: Pharm. Zentralhalle 65, 557 (1924).

# WINTERNITZ TEST FOR PANCREATIC INSUFFICIENCY

Five cc. of ethyl iodobenzoate are ingested by the patient during a meal. On the non-appearance of iodine in the urine within 24 hours, insufficiency of the pancreas may be safely assumed.

Reference: Münch. med Wochschr. 1913, 775.

# WISTARIN

A chromo-glucoside from bark of *Wistaria sinensis*; a yellow crystalline powder; m.p. 204°; toxic, causing diarrhea followed by collapse.

# WITCHES MILK

Milk produced by infants or by men with endocrine disturbances.



# WOLFFIAN BODY

Mesonephros; the primitive excretory organ of the embryo.

# WOOD GUM

The crude extract of wood and straw with caustic soda, of which xylan is the chief component.

# WOOLSORTER'S DISEASE

See Anthrax.

# WORENINE

An alkaloid,  $C_{18}H_{18}NO(OCH_2O)_2$ , from root of *Coptis japonica*; it is probably  $\beta$ -methyl-coptisin.

# WORMS, INTESTINAL

Parasitic infections of the intestine. These may be: (1) tapeworm (2) roundworm or (3) pinworm. There are many types of tapeworm originating from beef, pork, fish or adapted to other animals than man. They range from 1 inch to 20 feet in length. After dietary preparation, etc., anthelmintics are administered. These are: oleoresin of aspidium, a chlorinated hydrocarbon like carbon tetrachloride, pelletierine tannate, pumpkin seeds. Roundworms or eelworms (*ascaris lumbricoides*) invade in large numbers and are treated with hexylresorcinol, oil of chenopodium, and the specific, santonin. Pinworms (seatworms, threadworms, oxyuris) caused strong anal itching. The remedies used are: gentian violet, hexylresorcinol and other anthelmintics if necessary.

# WOUND HEALING

The cells of the body are capable of repairing sublethal individual injuries. In addition, some tissues proliferate to replace lost cells. Reparative ability is lowest in muscle and cartilage, which have their defects filled in by fibrous tissue. Injuries to nerve fibers may be

followed by regeneration, whereas the cell body is more susceptible. Repair in other tissues is featured by cell proliferation as well as by the recovery of cells not too severely injured. The details of the healing process in neurones and the several types of connective tissue cannot be discussed here. Attention will be directed solely to the healing of wounds as it occurs where epithelium and a fibrous substrate enter into partnership. Most of the information, both old and new, deals with skin wounds, and the statements made hereafter will refer chiefly to this type. However, repair of the serous and mucous surfaces differs in no fundamental way from that on the external surface.

## I. TYPES OF REPAIR

### 1. Primary

In this form of injury the wound is superficial or cleft-like. It may be repaired: (a) By simple epithelial regeneration alone, if no deeper tissues are involved. (b) By the direct adherence of the sundered surfaces, after which uncomplicated regeneration of epithelium and of connective tissue (cicatrization) takes place. This subtype, in particular, is often designated as 'healing by primary intention.' (c) By healing under a scab which provisionally closes a wound; this is 'primary scab healing.'

### 2. Secondary

In open wounds, involving gross defects, cicatrization is preceded by the building up of 'granulation tissue,' each granule representing a minute vascular territory that consists of newly formed, vertically upstanding blood vessels, surrounded by young connective-tissue and wandering cells of different kinds.



Such repair of dermal elements, accompanied by concurrent epithelization, can also take place under a scab (secondary scab healing). The name 'healing by secondary intention' has often been applied to secondary healing, and especially when suppuration accompanies the granulation process.

## II. THE EVENTS OF WOUND HEALING

### 1. Provisional Closure

(a) The fresh wound: Tissues, previously continuous, are separated and the wound often gapes because of mechanical retraction. In deep wounds blood vessels are opened and more or less hemorrhage follows. Nutritive disturbances are naturally set up in regions deprived of their normal blood supply. Many cells are killed outright by the wounding agent; others, to variable distances, are traumatized and may eventually succumb or recover.

(b) Cessation of the blood flow: Clotting at the wound site, contraction of the wall of blood vessels and capillaries, and temporary diversion of the blood stream around and away from the site of injury—all these lead to the control and stopping of hemorrhage. Thrombosis is a minor factor and, possibly, is even negligible or lacking. There is considerable evidence that even large, severed arteries at times undergo segmental spasms, contraction and retraction of the wall, and detachment and rolling-up of the intima; these spontaneous activities may lead to cessation of the blood flow in the entire absence of thrombus formation.

(c) Traumatic inflammation: Some inflammation always follows a penetrating injury and precedes

the repair of connective tissue. Its extent depends on the nature of the wound. It is characterized by hyperemia, exudation, leucocytic emigration, etc. These phenomena lead to a provisional covering of the wound surface by fibrin, and later to the removal of noxious substances, to the resorption of blood and other exudates, and to the removal of degenerating tissue fragments through phagocytosis and enzymic digestion. This second group of activities extends over into the important stages of degeneration and repair.

(d) Closure by apposition: Clotting is of prime importance by providing a provisional closure of the wound. In cleft-like wounds (including approximated operative wounds) the amount of blood clot is limited, but there is a sufficient fibrin sheet to close the wound, to stick the apposed surfaces together, and to offer an excellent scaffolding for invading, new cells.

(e) Closure by scab formation: Open wounds are soon closed, sometimes within a few minutes. Coagulation produces a fibrinous mass which is at first a mere jelly-like filter that restrains the more corpuscular and viscous constituents of the blood. Contraction and drying change it to an impermeable, protective crust or scab. This process is a typical example of syneresis.

### 2. Destructive Changes

In the absence of complications this period is usually short. It includes chiefly the death and removal of injured cells and the absorption of exudates.

(a) Zones of injury: A first zone is that in which tissue is destroyed

directly by the wounding agent. The second zone, next remote, contains tissues subject to traumatic necrosis. Farthest distant is a third region whose cells have been subjected to molecular violence; necrobiosis or recovery may follow. The first and second zones are contaminated by microorganisms. The second and third zones do not contain tissues of full vigor; this lowered vitality is related both to bacterial advance and to subsequent repair.

(b) Tissue destruction: This may result directly from traumatization or indirectly through metabolic deficiencies resulting from vascular injuries. The secondary destruction is accomplished chiefly by autolysis and heterolysis. Autolysis acts through enzymic (pepsinase; peptase; arginase; etc.) activities traceable to the declining cells themselves. Heterolysis, produced by leucocytic enzymes, occurs chiefly in the necrotic zone and hence is most evident in infected wounds. Only the neutrophiles are known surely as enzyme-bearing agents. Leucotryptase can only attack dead cells and altered connective-tissue fibrils; it also aids in the removal of fibrinous deposits. Isolysis, resulting from enzymic influences emanating from sound cells, and alolysis, resulting from dissolution effected by chemical substances (such as lye or bacterial enzymes) foreign to the normal body, may also have importance. Phagocytosis plays a definite part during the destructive period. Macrophages remove tissue debris and fibrin; neutrophiles possibly aid by engulfing the smaller particles.

(c) Reparative stimuli: Tissue hunger, resulting from inadequacies of oxygen and of nutritive substan-

ces, supplies a stimulus that induces cell division and some other activities. The products of cell destruction, likewise, can be stimulatory. Considerable has been written regarding 'necrohormones' with this origin. Mention should also be made of the growth-promoting substances (trephones) elaborated by leucocytes and also found in embryonic juices. Interest in the stimulatory effect of protein decomposition products has been reawakened by claims for the primacy of the sulphhydryl radical as the causative agent that induces proliferation.

(d) Wound secretions: The unmodified blood and lymph that flows from a wound is changed in composition and amount as fibrin is deposited. As in ordinary inflammation, the more viscous constituents (fibrinogen; globulin) are especially increased during the first day after wounding occurs, but within a few days the wound fluid consists principally of albumin. The secretion of an open wound is always distinguished from lymph by a significantly higher protein content and by a considerable admixture of leucocytes. A healthy, granulating wound has a scanty secretion, mucoid in nature and with but a few leucocytes.

(e) Role of infection: Every accidental wound contains introduced bacteria. The course of the resulting infection governs the length of the destructive period, and this is the dangerous phase in wound healing. But wounds treated within the first six to eight hours can usually be turned into as favorable a course as those produced by aseptic surgery.

### 3. Constructive Changes

The reparative phase follows, but overlaps, the destructive period.

Secondary infections or other disturbances may cause the constructive events to suffer relapses, or even to give way temporarily to destructive recurrences.

#### A. Connective-Tissue Participation

(a) Cells involved: These are the types characteristic of loose connective tissue, together with some derivatives aroused into being by the inflammatory stimulation.

(b) Primary healing: The connective-tissue and endothelial cells are proliferating abundantly by the second day. Cells and vascular sprouts collect in the wound wall and then extend from wall to wall. Fibrin is resorbed and connective-tissue fibers are laid down to restore lost continuities. A decrease in cellularity and vascularity results in the formation of typical scar tissue.

(c) Secondary healing: In about six to eight days, open free wounds begin to fill with granulation tissue. This is a highly vascular, embryonic type of cellular material that appears pebbly in surface view. Each 'granule' has a vascular tree as a core, and this is enveloped by a mantle of wandering cells and young fibroblasts. The sheet of early granulation tissue provides a cellular, protective membrane that supplants the provisional fibrin layer. It is less permeable than the fibrin layer and it provides an excellent defense against infection.

Healing by granulation tissue presents a diverse picture in comparison with the uniformity shown by aseptic, cleft-like wounds. Many factors may operate against the production of 'good' granulation tissue. In large wounds the growth force of the regenerating tissue may even

exhaust itself so that an ulcer results.

(d) Fibroplasia: In aseptic, apposed wounds, connective-tissue fibrils appear within a few days. In open, granulating wounds fibroplasia begins when the destructive period is ended, when all the dead and foreign materials are removed, and when the fibroblasts are mature. The earliest fibrils deposited are sparse, delicate and rich in water. The ends of old, severed fibers are reunited by a 'splice' of new fiber. This requires a swelling and solution of the formed, collagenous substance of the old fiber at the level where it joins the new. The exact manner of origin of connective-tissue fibers (intracellular vs. intercellular) is an ancient controversy, still debated.

(e) Scar tissue: The speed of cicatrization depends on factors such as the size and nature of the wound, and the freedom from infection and other complications. Surgical wounds, with good apposition, heal promptly. The progress of fibroplastic repair can be measured on the basis of the return of tensile strength. Wounds of the skin, fascia and stomach regain their normal strength in two weeks. The young scar is at first rich in cells and blood vessels, and only gradually does it revert to the paler, less vascular and less cellular permanent tissue. Elastic fibers appear slowly, after some months. Although the young scar spreads somewhat, after epithelial healing is completed, it eventually shrinks.

#### B. Epithelial Participation

(a) Method of repair:  $\alpha$ . Excoriations, burns and blisters: When the injury is confined to the epidermis the superficial, lost cells are replen-

ished directly from the deeper layers.

β. Cleft-like wounds: If the incision cleanly made, with apposed edges that stick together, the restoration of epidermal continuity and the resumption of conformity between its constituent layers may be completed at the end of one day.

γ. Gaping or stitched wounds: Due to the faulty approximation of edges, considerable cell migration is necessary. Mobilization begins within one hour and soon tongue-like processes are extending over the fibrinous substrate. The time required to bridge the defect naturally depends on its size and the obstacles encountered.

δ. Scab wounds: More complex is epithelial repair in primary or secondary healing in which a scab is formed. Many factors serve to vary the details of this process, as well as its rate. The granular and horny layers of the epidermis, at the margin of the wound, resolve into a syncytium with dark, rod-like nuclei. This composite tissue is the fastest-moving of all the epidermal components. It rapidly makes a covering to the whole scab, and even at 36 hours this is well along toward completion. Arms of the same syncytial layer also invade the scab from the sides and from above downward, and dissolve it—including islands of blood encountered along the way. The cells of the Malpighian layer assume an elongate spindle shape, and cell boundaries become indistinguishable. These elements both invade the scab from the sides and also pass beneath it. The deeper portion of the new epithelial mass is retained when the more superficial scab falls off. It then serves as the

basis of the definitive epithelial covering.

ε. Granulating, scabless wounds: The slowness, variability and complexity of epithelial repairs in this type of wound are concomitants of its open nature and large size. The growth tendency of connective tissue is restrained as it becomes covered with the epidermis. The Malpighian cells are apparently the responsible agents in this, but the nature of the antagonism is unknown.

(b) Mechanism of closure: α. Role of migration: The chief factor in epithelial expansion over a denuded area is amebism. The migratory movement apparently is more or less of a mass nature. If a wound area is small enough, it will be completely epithelized before cell division plays any part, or can play any part because of time limitations. Epithelial migration is based on amebism that utilizes a stereotropic response, by which the cells cling to the substrate, and a centripetal directional growth that is related to a polarization with respect to cells that face a foreign environment in one direction and remain in contact with other cells in the opposite direction. Thus it is that epithelial growth continues until the effect of the foreign body is removed; that is to say, until the wound is covered and the clot is organized.

β. Role of proliferation: Mitosis is a tardy, rather than an early phenomenon in healing. In fact, there may be an actual decline below the normal mitotic frequency during the first days following an injury. In small wounds mitosis is always secondary; it comes late to restore depletion caused by the



primary cell migration. In larger wounds, with a longer healing period, there are few mitoses at first in the epithelium that is moving centripetally to cover the defect; later they increase and reach a maximum at the time of closure. At the periphery of the wound, however, mitoses do increase markedly in the old epithelium (and especially at the wound margin) as long as the wound remains open. The number is usually proportionate to the quantity of cells that have moved into the defect.

γ. Role of volume increase: During repair the epithelial cells and their nuclei increase in size both in the new covering and about the wound margin. This gain of some 35 per cent contributes in a minor way both to the forward extension of the epithelial ingrowth and to its thickness.

δ. Role of contraction: This factor is important in wounds of the loose skin that are more than 10 mm. in diameter. After several days, in man at least, contraction of the floor of granulation tissue begins to draw together the margins of the wound. This contraction continues until the edges of the epithelium are about 10 to 15 mm. apart.

### III. MENSURATION

The course of normal wound healing follows a curve that is subject to mathematical expression. Since there are definite relationships between such factors as the size and age of the wound, the age of the patient, etc., the rate of healing becomes determinable and its day-by-day course and termination are predictable. The data, as used, apply to uninfected wounds in loose skin from which areas more than

10-15 mm. in diameter have been lost. Four periods are recognized:

1. Latent period: After a wound has been produced it remains for a time practically unchanged in size. The duration of this phase varies between 1-2 days and 4-5 days, but its length can be prolonged or shortened by various controllable means.

2. Contraction: Following the latent period, the wound decreases in size by a centripetal closing-in process. The rate is directly proportional to the size of the wound. Rapid at first, it slows progressively until the edges of the wound are 10-15 mm. apart. Nevertheless, if the wound is originally larger than 40 mm. the contraction often stops when the reduction has reached 20-25 mm. The phenomenon of contraction is of little or no moment in wounds less than 15 mm. in diameter.

3. Epidermization: Although a later stage than contraction, epithelial resurfacing may overlap it to some extent. The commencement of epidermal ingrowth depends on the size of the wound area to be covered. It makes a tardier appearance in large wounds, and growth is exceedingly slow if the distance to be covered is more than 12-15 mm. In fact, epithelization comes to a halt and is incomplete if the edges of the wound are still some 20-25 mm. apart when contraction has reached its limit. On the other hand, wounds less than 10 mm. wide are covered rapidly. The rate of epidermization is inversely proportional to the size of the wound; hence the speed reaches a maximum toward the end of healing when the edges approach.

4. Cicatrization: This extends

over a relatively long time and brings the healing process to an end. As the result of contraction, already described, the scar is proportionately smaller in large than in small wounds. When the wound is small enough (10-12 mm.), so that contraction never appears, then wound and scar are the same size. Following epithelial healing there is some enlargement of the scar by spreading, but the end result is a shrinkage of the scar tissue.

#### IV. PHYSICO-CHEMICAL RELATIONS

The chemical phenomena related to wound healing are less well known than are the structural features. Some of the more pertinent information will be summarized:

1. Fluid content of wound tissues: The tissues of cleft-like and gaping wounds contain more than the normal amount of fluid. Maximum hydration is attained in one day and a gradual decline then follows. How an approach to the more sol-like condition of fetal tissues is brought about in the wound (physical absorption or hydrolysis) is not entirely understood.

2. Electrolytes: Increase in the water content of the wound territory brings a concomitant influx of electrolytes, in which the greatest individual storage is of potassium.

3. Electric potentials: It might be expected that with the production of pronounced changes in the colloidal condition of wound tissues and with the creation of many active surfaces that differences in electrical potential would appear. Especially is this true of granulating wounds. There is a constant electric current in such wounds

whereby the granulation tissue is positively charged with respect to the neighboring skin. The strength of the current bears a relation to the exuberance of granulation tissue. In simple surgical wounds the electrometric method can be used to record the course of fibroplasia and to indicate the attainment of maximum tensile strength by the new collagenous fibers.

4. Mitogenic radiation: It has been claimed that cells or cell extracts are capable of emitting 'mitogenic rays' (identical with ultra-violet light) which will induce mitosis in other cells. These claims, however, have been strongly contested.

5. Hydrogen ion concentration of wounds: Stasis in the blood vessels leads to an accumulation of carbon dioxide which brings about a local acidity. The resulting oxygen-want also effects an alteration of the cellular metabolism in which organic acids are elaborated. Since these products are not transported away efficiently, the local acidity is correspondingly increased to a further degree. As might be expected, the shift toward the acid side is greater in the early stages of healing. In contrast to acid values in the deeper levels of granulating wounds or under scabs is a secondary alkalinity of the surface secretion due to the evaporation of carbon dioxide.

6. Influence of diet on pH: A sure change of values under the influence of acid or alkaline diet has not been established by measurements. Nevertheless, there is a definite increase in the carbon dioxide binding-power under alkaline diet and a corresponding decrease under acid diet. The quan-



tity of wound secretion is regularly and considerably scantier under acid diet. This has been interpreted as due to an increase in the oncotic pressure in the compensatory acidosis of blood, whereby there is a marked swelling of the blood corpuscles and a resorption of tissue fluid in the capillary region. In blood alkalosis the opposite occurs and exudation is favored. The kind of food eaten influences the course of wound healing and an acid diet is favorable in this regard.

7. Effects of acidity on wounds: Both the structural and the metabolic changes are qualitatively similar in wound healing, tissue transplantation and inflammation. It seems safely established that the reaction in the wound area, and especially in the earlier stages, is pushed toward the acid side. Through this local acidity several favorable conditions are produced:

(a) Enzymic autolysis: One optimum for the activity of proteolytic enzymes lies at pH 6.4. This value lies in the neighborhood of the acidity existing in the wound area.

(b) Mitogenic radiation: The intensity of the ultraviolet radiation, said to emanate from the products of tissue proteolysis and to be of significance as stimulators of cell division, is claimed to increase with the acidity of the medium.

(c) Capillary dilatation: Limited acidity, such as is found in wound healing, induces capillary dilatation. Mechanical compression of vessels follows the retraction and volume increase of severed connective-tissue bundles, and this leads to stasis. Moreover, traumatism of the nerve supply and muscle of blood vessels

may result in the expansion of capillaries. Concurrent with capillary dilatation goes a slowing of the blood flow and the collecting of leucocytes on the capillary wall. Emigration of the leucocytes is favored by the colloidal loosening of the endothelium through H-hyperionia. Acidity is also favorable for phagocytic activities.

(d) Transmission of plasma colloids: The swollen capillary wall becomes permeable to plasma colloids in the same way as occurs in acute inflammation. Yet the associated changes taking place in these colloidal membranes are not surely understood. The albumin, globulin and fibrinogen of the plasma show decreasing permeability in the order listed. Probably the egress of colloidal substances is explained on the basis of increased vascular pressure and heightened permeability of the endothelial wall; a secretory activity by the capillary endothelium has not been proved and is held to be improbable.

(e) Swelling of tissue colloids: Some, but not all, of the phenomena exhibited in the swelling of colloids are related directly to the degree of acidity at the wound site. In general, tissue colloids swell when there is an increase of H-ions. Whereas mature collagen behaves in this manner, Wharton's jelly (as a type of embryonal tissue) is said to swell in an alkaline medium and to shrink in an acid one. Moreover, fibrin exhibits minimal swelling at the acidity of the early, healing wound; as this acidity subsequently recedes, the condition is favorable to the swelling and solution of the fibrogel.

(f) Pain: Although acidity is related to pain, it is not the only

factor involved. The injection of buffered acid phosphate solution into the normal skin can be exceedingly painful for a short time until the buffering action of the blood restores the normal tissue reaction. Although in aseptic wounds continued acidity cannot exist, yet in inflamed wounds there is a possibility of strong pain on the basis of local acidity. Indeed, this can be relieved by the injection of buffered alkaline phosphate solution.

8. Metabolism of wound tissues: Study of respiration and anerobic glycolysis in aseptic wounds shows that shortly after the infliction of a wound the metabolic rate falls in the wound area. This decline corresponds to the destructive phase of the healing cycle. The ensuing shift to a metabolic rise coincides with the arrival of ameboid cells from the blood and connective tissue; it characterizes the second, or assimilative, phase. Finally, as a third phase, comes the decline of the wound metabolism to a normal level.

## V. FACTORS INFLUENCING HEALING

1. Age: It is well known that the age of the patient has a strong influence on the rate of healing. Age can be expressed in terms of a constant, which, in a formula of healing rate, corresponds to the person's physiological activity. The rapidity of healing in younger individuals is usually said to be due to an actual increase in the rate of cellular proliferation. Another interpretation is that repair begins earlier and is less retarded in the young.

2. Mechanical pressure: Mild pressure is said to be favorable to healing by eliminating dead spaces,

controlling oozing, limiting blood and lymph stasis in the tissues, and limiting the amount of plastic substance that pours into the wound. It is also claimed that a pressure that blanches the granulation capillaries, restrains the growth of connective tissue yet permits epithelial growth to proceed unaffected.

3. Temperature: In some cold-blooded animals the healing rate doubles when the temperature is raised 10° C. Also in mammals it would appear that the velocity of the reparative phenomena depends upon the rate at which certain chemical changes take place. Under special conditions temperature can doubtless become a factor that alters this rate. It may explain in part the favorable results on healing produced by sympathectomy; a definite increase in the warmth of the affected part accompanies the resulting hyperemia.

4. Sympathectomy: There is rather general agreement that the elimination of the sympathetic nerve supply to a region has an accelerating effect on wound healing. This benefit is signaled by both vasodilatation and increased temperature.

### 5. Radiant Energy

(a) Ultraviolet light. According to most observers a mild degree of exposure reduces the healing time of wounds. The beneficial influence would apparently be related to factors other than a simple germicidal effect. It has been suggested, with some evidence, that the radiated cells react by producing substances that stimulate cell proliferation.

(b) Roentgen rays: In spite of contradictions, perhaps largely the result of diverse experimental con-

ditions, it would appear that small doses stimulate healing. The re-large, early doses retard. The re-tarding effect is exercised more on connective tissue than on epi-thelium.

6. Diet: Inadequate diet retards healing only in young animals. Yet diseases that affect the general metabolism (e.g., diabetes) are unfavorable to wound healing. The beneficial effect of an acid diet is generally conceded. With open wounds it acts by shortening the latent period. In approximated, stitched wounds the latent period is not influenced, as measured by the return of tensile strength in regenerating connective tissue, but the velocity of fibroblastic repair increases and maximum strength is, therefore, regained earlier.

7. Vitamins: The role of vitamin C is safely established, while the reported beneficial effect of other vitamins may prove illusory. Deficiency of vitamin C delays healing or even prevents it from reaching completion. In scurvy the proliferative ability of connective tissue cells is unaffected, but the fibroblasts do not mature and the inter-cellular substance (collagen) is not deposited. Neither is collagen maintained properly under these conditions; even old scars may soften and wounds disrupt. The administration of ascorbic acid is followed by prompt fibroblastic healing. In vitro studies on fibroblast cultures demonstrate a sudden increase in collagen fibrils when ascorbic acid is added to the medium.

8. Hormones: There is some reason for the belief that injured cells produce hormone-like substances that accelerate the healing of wounds. But, in addition, claims

have been made for the beneficial results that follow the local application of sliced or pulped endocrine glands, or their extracts, to wound surfaces. It would appear that these experiments have contained too many uncontrolled factors to merit confidence.

9. Infection and disease: Chief among the common factors that delay healing is infection. Even a distant abscess has been held responsible for such delay. Reports of the unfavorable influence of various systemic diseases are numerous. Diabetes is a known offender, while syphilis has been suspected by some.

10. Topical agents: Some of the preceding paragraphs touch on the local application of presumably beneficial agencies. Thus, sympathectomy and its results are fairly well localized. Radiant energy may be, and in the case of the Roentgen ray has been, applied locally. The tissues of endocrine glands have been applied as poultices while their extracts have been painted on or used as salves. Among other topical agents that have been employed are inert agents, antiseptics and supposed stimulants. The first two groups are not proven to be advantageous. With respect to the last group, benefits have been claimed from the use of urea or allantoin, from substances containing sulphhydryl, and from embryonic extract. These claims have, however, not remained unchallenged.

## VI. THE NATURE OF THE FORMATIVE STIMULUS

This might be either something that directly promotes growth or something that removes an obstacle to growth. Both ideas have been

championed, but the former has enjoyed greater popularity. Among the arguments for 'wound hormones,' and so on, produced from injured cells, has come a line of reasoning that started with the growth-promoting tendency of embryonic tissue-juices, went on to trace the agent through the higher cleavage products of certain proteins, concluded that the growth-promoting ability should be attributed to the ease with which tissue juice can be transformed into peptides by tissue enzymes, and finally settled on the sulphhydryl radical as the essential principle that is responsible for cell multiplication in both animals and plants. But proliferation is not the only feature of repair. The differentiation of formed products is a markedly different thing. The dependence of collagen on vitamin C seems safely established; ascorbic acid perhaps controls the deposition of intercellular substance by being responsible for the setting or jelling of a liquid product. It is safe to predict that the remarkable ad-

vances that have been made toward the analysis of the fundamental factors responsible for wound repair will be transcended by further, and more intimate, knowledge in the future.

## VII. REFERENCES

The bibliography of wound healing is voluminous. A fairly extensive set of key references to the various phases of this topic will be found in a review published by the present writer in *Physiological Reviews*, Vol. 16, No. 3, pp. 327-406. There is no other equally comprehensive and selective bibliography.

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## WOUND HORMONE

See Plant Growth Hormones.

## WYSS DETERMINATION OF INSULIN

Insulin retards or prevents the hydrogen peroxide oxidation of glucose or of phenols.

Reference: *Compt. rend.* 181, 327 (1925).

## X

### XANTHEOSE

See Theobromine.

### XANTHINE BASES, TESTS FOR

See Burian.

### XANTHERINE

$C_{24}H_{28}O_6N$ ; an alkaloid occurring in two forms in the bark of *Xanthoxylum ochroxylum*; paralyzes the nervous system.

### XANTHINE

Ureous acid; xanthine oxide; 2:6-oxypurine, an intermediate in nucleoprotein metabolism, formed from guanine by the enzyme guanase or from hypoxanthine by oxidation, and itself oxidizing to uric acid.

### XANTHINE OXIDASE

Milk flavoprotein; aldehyde oxidase; dihydrocoenzyme I oxidase; Schardinger enzyme; a flavoprotein enzyme catalyzing the oxidation of certain purines, aldehydes, hypoxanthine and xanthine to uric acid, the dismutation of xanthine to uric acid and hypoxanthine, etc., m.w. about 280,000 (milk); various differences depending on the source remain to be explained.

### XANTHOMATOSIS

See Eye, Biochemistry of.

### XANTHONES

The name given to the class of

plant pigments derived from xanthone or benzophenone oxide, anthoxanthes. See Flavones.

### XANTHOPHYLL

(1) A name for the companion of carotene consisting of two isomers, lutein and zeaxanthin, oxidation products of alpha and beta carotene respectively;  $C_{40}H_{56}O_2$ ; (2) a general name for yellow pigments which are oxidized carotenoids, soluble in methanol.

### XANTHOPROTEIC TEST

A test for proteins containing amino-acids with a benzene nucleus, depending on the yellow color produced with conc. nitric acid, turning to orange on being made alkaline.

### XANTHOPTERIN

Yellow pigment of butterfly wings,  $C_{18}H_{18}O_6N_{16}$ .

### XANTHORHAMNIN

Rhamnin;  $\alpha$ -rhamnegin; glycoside of Persian berries, hydrolyzable to rhamnetin and rhamninoase, a triose.

### XANTHOSE RIBOSIDE

See Xanthosine.

### XANTHOSINE

Xanthose riboside; a nucleoside consisting of d-ribose and xanthine, formed by the deamination of guanosine.

**XANTHOTOXIN**

$C_{11}H_5O_3 \cdot OCH_3$ ; m.p. 145-146°; a cyclic "bitter principle" of fruit peel of *Fragaria xanthoxyloides*, a fish poison.

**XANTHOXYLUM**

Dried bark and full grown berries of *Xanthoxylum americanum*; used as carminative and mild diaphoretic.

**XANTHYDROL**

A precipitant for urea, which also precipitates allantoin and allantoic acid.

**X CHROMOSOMES**

Chromosomes responsible for sex determination.

**XEROPHTHALMIA**

See Eye, Biochemistry of.

**XEROPHYTES**

Plants adapted to growth and survival under a scarcity of water or draught. They are often thorny and supplied with thick rinds or cuticles.

**X-RAY DIFFRACTION OF PROTEINS**

See Protein Structure.

**X SUBSTANCE**

Substance which intensifies the action of testosterone, which probably accompanies it.

**XYLAN**

A hemicellulose of bran, straw, wood, which yields xylose on hydrolysis.

**XYLANASE**

An enzyme which hydrolyzes xylans to xylose.

**XYLEM**

Woody portion of plants between pith and cambium.

**XYLENOL BLUE**

p-Xylenolsulfonphthalein; 1,4-Dimethyl - 5 - hydroxybenzenesulfonphthalein; used as indicator changes being red at pH 1.2, yellow at 2.8, and blue at 9.6.

**XYLINIC ACID**

An acid produced from xylose by *Bact. xylinum*.

**XYLOKETOSE**

See Glycosurias, Non-diabetic.

**d-XYLOSE**

A pentose of straw, bran, hemicelluloses, some glycosides (primerosides), m.p. 153°, not fermentable.



## Y

### YAJEINE

A toxic alkaloid,  $C_{14}H_8N_3O$ .

### YANGONIN

An amaroid,  $C_{15}H_{14}O_4$ , from Kava root, crystallizing in yellowish prisms; m.p., 153-154°.

### YAWS

Frambesia; an infectious disease caused by *Treponema pertenue* (Castellani) resembling the spirochete of syphilis. The lesions resemble raspberries (=frambesia). Contagiousness is very high. Arsphenamine or neoarsphenamine with bismuth and iodine preparations are used as specific therapy.

### YEAST

The living cells of the species of *Saccharomyces*; in commercial form, it is usually combined with a starchy or absorbent base appearing as white, soft, easily broken masses of a characteristic slightly sour odor; used as antineuritic in B avitaminosis; also effective in treatment of acne, indigestion, flatulence, furunculosis, constipation; when irradiated acquires antirachitic properties; stimulates leukocytosis.

### YEAST GROWTH FACTOR

See Pantothenic Acid.

### YEAST GUM

Probably chiefly a mannose polysaccharide, made by enzymatic degradation of yeast or by extraction with caustic and precipitation with Fehling's solution.

### YEASTONE

A purified, concentrated extract of yeast containing the active principles of yeast but without vitamin; used in same way as yeast except in B avitaminosis.

### YELLOW FEVER

An infectious disease due to a virus transmitted by the mosquito, *Aedes aegypti* (*Stegomyia*). A condition of jaundice follows fever, albuminuria and hemorrhages. Quarantine against the mosquito is practiced as prophylaxis, but there is no specific treatment for the disease.

### YELLOW RESPIRATION ENZYME

Lactoflavinphosphate ester with a specific protein.

### YERBE MATÉ

Leaves of a Paraguay tree which produce beverage like tea.

### YLANG YLANG OIL

Cananga Oil; a volatile oil distilled from the flowers of *Cananga odorata* containing geraniol and linalool esters of acetic and benzoic

acids and other compounds; used in perfumes.

**YOECA**

A caffeine containing drug of the bark and stems of Yoea.

**YOGHURT**

Bulgarian curdled milk; said to displace harmful intestinal bacteria.

**YOHIMBENE**

Isomer of yohimbine( q.v.) m.p. 278°, from the bark of the African corynanthe.

**YOHIMBINE**

$C_{21}H_{26}O_3N_2$ , an alkaloid of the African corynanthe yohimbe and Argentine quebracho, m.p. 235°; used as aphrodisiac; other names: quebrachine, corynine, aphrodine, hydraergotocin.

**YOLK**

Nutrient material of egg; vitellus, ooplasm; deutoplasm.

**YOUNG TEST FOR COCAINE IN THE PRESENCE OF NOVOCAINE**

Four-five drops of 2% cobalt thiocyanate are poured over a small portion of the solid. Dark blue flocks form if only cocaine is present. If novocaine is also present, the whole solution turns blue. Four-five drops of freshly prepared stannous chloride solution (10 gm. stannous chloride and 5 gm. metallic tin in 100 cc. 1:1 hydrochloric acid) are added; in the presence of novocaine alone, the precipitate dissolves; if only cocaine is present the blue flocks remain unchanged.

Reference: Am. J. Pharm. 1931, 709.

**YUCCA FRUCTOSAN**

A fructosan of Yucca mohavensis, Sarg., similar to graminin of rye flour.

## Z

### **ZAPPACOSTA TEST FOR INDOLE AND SKATOLE IN BLOOD**

An acetic acid solution of blood serum is treated with trichloroacetic acid; indole and skatole are indicated by a reddish-blue color which may also be used for colorimetric estimation.

Reference: *Diagnostica tec. lab.* (Napoli) Riv. mens. 6, 870 (1935).

### **ZEA**

Corn Silk; consists of maizenic acid, fixed oil, resin, mucilage; found in fresh styles and stigmas of Zea Mays; used as demulcent, i.e. in urogenital diseases.

### **ZEAXANTHIN**

A carotenoid found in yellow Zea Mays. Its structure is 3-3'-dihydroxy- $\beta$ - $\beta'$ -carotene, m.p. 207°.

### **ZEDOARY**

Dried rhizome of *Curcuma Zedoaria* containing resin, volatile oil, starch, mucilage; used as a stomachic like ginger in dyspepsia and flatulence.

### **ZEIN**

A prolamine of maize seeds, lacks lysine and tryptophane, m.w. about 35,000.

### **ZEOLITES**

Minerals which are essentially hydrous silicates of aluminum which

usually contain sodium or calcium and sometimes barium, strontium, potassium and magnesium. They are employed in ion exchange or for the adsorption of complex organic compounds, like vitamins, from solutions.

### **ZEPHIRAL**

An aqueous solution of a mixture of high-molecular alkylbenzylammonium chlorides; used as a bactericide in surgery, obstetrics and dermatology.

### **ZIMMERMAN PRECIPITANT FOR PHYSIOLOGICALLY IMPORTANT BASES**

Arginine, creatinine, betaine, choline, histidine, etc., form difficultly soluble salts with rufanic acid (1,4-dihydroxyanthraquinone-2-sulfonic acid).

Reference: *Zeit. physiol. Chem.* 188, 180.

### **ZIMMERMAN REACTION FOR HISTIDINE**

0.2 mg. histidine hydrochloride, in a 1 cc. Thunberg tube, is treated with 3 drops of 1% cobalt nitrate solution. A small tube containing 10 drops of 2N sodium hydroxide is inserted, the tube evacuated and the solutions mixed. A violet color develops. Reference: *Zeit. physiol. Chem.* 186, 260 (1930).

**ZIMMET REAGENT FOR REDUCED GLUTATHIONE AND OTHER SULFHYDRYL COMPOUNDS**

Sodium nitroprusside reacts with glutathione but not with acetone within a very narrow pH range (about 9). A reagent having the proper pH is made up of 5 gm. sodium nitroprusside, 50 gm. sodium phosphite and 100 cc. water and gives a red color with very dilute glutathione solutions. Reference: Compt. rend. soc. biol. 113, 984 (1933).

**ZINC TEST**

See Hahn.

**ZINGERON**

Zingiberon; m.p. 40-41°; 3-methoxy-4-hydroxy-phenyl-ethyl-methylketone; a constituent of oil of ginger.

**ZINGIBER**

See Ginger.

**ZINGIBERON**

See Zingeron.

**ZONA PELLUCIDA**

A membrane surrounding the ovum; ovolemma.

**ZOOBLAST**

Animal cell.

**ZOOCHEMISTRY**

See Biochemistry (Definitions).

**ZOOERYTHRIN**

Red pigment of feathers.

**ZOO-FULVIN**

Yellow pigment of feathers.

**ZOOGAMY**

Sexual reproduction in animals.

**ZOOMARIC ACID**

Palmitoleic acid or hexadecenoic acid.

**ZOOMELANIN**

Black pigment of feathers.

**ZOOPHYTE**

An animal with plant habits.

**ZOOSTEROLS**

Sterols found in animal cells and tissues, e.g. cholesterol, dihydrocholesterol, 7-dehydrocholesterol, agnosterol.

**ZOOTOXIN**

Animal poison, as of snakes, wasps, etc.

**ZOOXANTHIN**

Yellow pigment of feathers.

**ZSIGMONDY GOLD NUMBER**

The concentration of colloid required to stabilize a standard gold colloid against precipitation by a standard NaCl solution.

**ZSIGMONDY GOLD REAGENT FOR COLLOIDS**

Reagent—When auric chloride is reduced by formaldehyde in the presence of a weak alkali, a red colloidal solution of metallic gold is obtained.

When the reagent is mixed with sodium chloride, it turns blue due to agglomeration of the gold particles, but certain colloids prevent this change. The amount required to prevent the color change may be used to classify colloids and is called the gold number.

Reference: Ann. 301, 29, Zeit. anal. Chem. 40, 697 (1901); 42, 676 (1903).

**ZULKOWSKY STARCH REAGENT FOR IODINE**

Sixty gm. of starch and 1 kilo of glycerin are stirred and gradually heated to 190°, until the mass is clearly soluble in water; this aqueous solution gives a blue color with iodine.

Reference: Ber. 13, 1396 (1880).

**ZWIKKER REACTION FOR  
PENTAMETHYLENETETRA-  
ZOL (CARDIAZOL,  
METRAZOL)**

A hydrochloric acid solution of cuprous chloride gives a crystalline precipitate with Metrazol even a dilutions of 1:40000.

Reference: Pharm. Weekblad 71, 1170 (1934).

**ZWITTERION**

An ion that is charged both positively and negatively; other terms are amphoteric ion and dipole ion, e.g. glycine which in solution has the form  $\text{—OOC—CH}_2\text{—NH}_3^+$ .

**ZYGADENINE**

$\text{C}_{39}\text{H}_{63}\text{O}_{10}\text{N}$ ; m.p. 200-201°; an alkaloid of the leaves of *Zygadenus intermedius*, Liliaceae; acts like veratrine.

**ZYGOTE**

See Gamete.

**ZYMASE**

The old name for a mixture of enzymes and coenzymes obtained from yeast juice free of cells, responsible for the alcoholic fermentation of glucose.

**ZYMO-EXCITOR**

A substance which activates a zymogen into the formation of an enzyme, e.g. HCl in the conversion of pepsinogen to pepsin.

**ZYMOGEN**

A precursor of an enzyme, e.g. as pepsinogen is to pepsin.

**ZYMOHEXASE**

A pyridinoprotein enzyme present in many plant, animal tissues and bacteria, which catalyzes the reversible splitting of fructose-1:6-diphosphate to 3-phosphoglycer-aldehyde and dihydroxyacetone-phosphate, and also the aldol condensation of dihydroxyacetone phosphate (dap).

**ZYMOID**

(1) Any poison derived from a decaying tissue; (2) a ferment or enzyme which has lost its power of decomposing the substratum but not its power of uniting with it.

**ZYMOSTEROL**

$\text{C}_{27}\text{H}_{44}\text{O}$  or  $\Delta^8:14,24:25$  cholesta-dienol, a secondary yeast sterol, dextrarotary, m.p. 108-109°; found in ergosterol residues.

**ZYMOTIC**

(1) A germ disease; (2) pertaining to enzymes.

**ZYTASE**

A malt enzyme which splits hemi-celluloses at pH 5 optimum; transforms xylan to xylose.